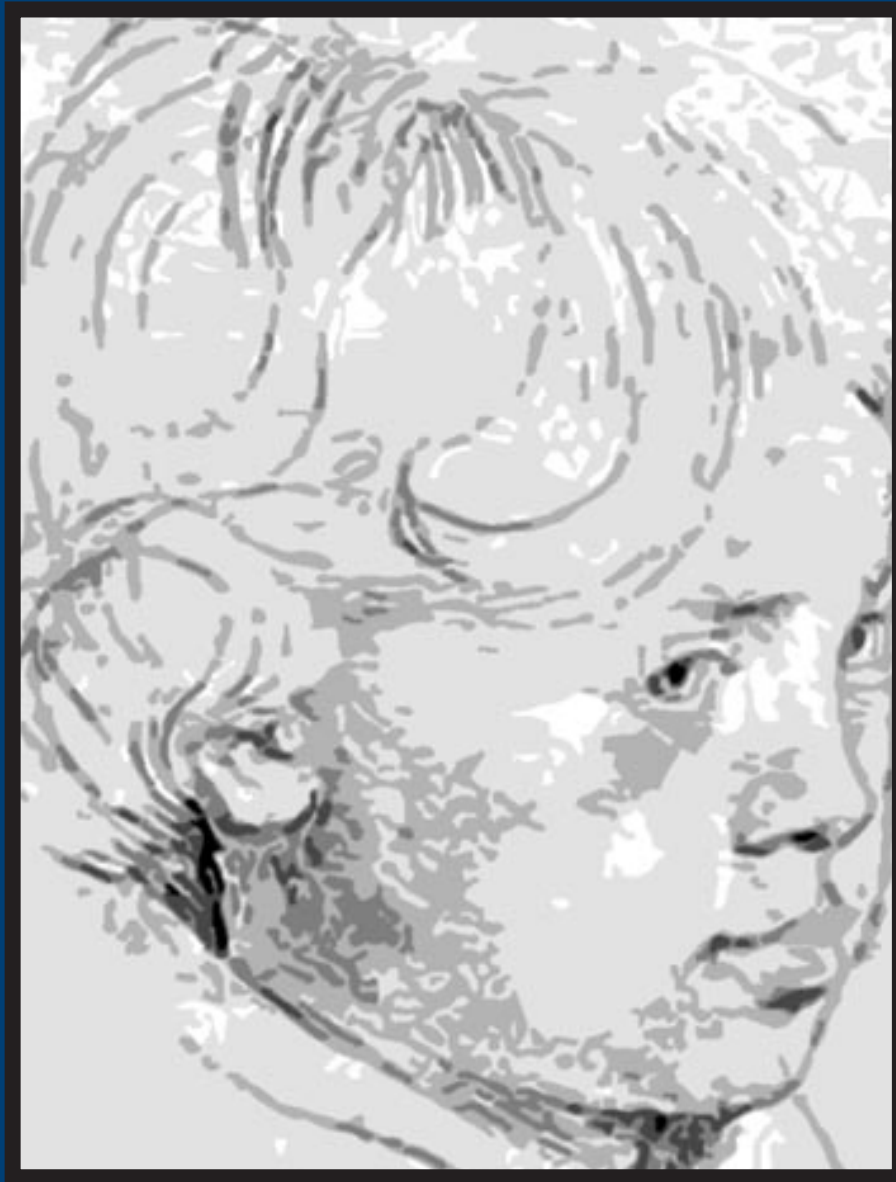


Task Force on Safer Childhood Vaccines

Final Report and Recommendations



National Institute of Allergy and Infectious Diseases
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Preface

This report distills evaluations and discussions by a group of public health experts on the topic of vaccine safety. The broad scope of the congressionally mandated charge forced equally broad analysis, congruent with other congressionally mandated actions focused on discrete components of the vaccine safety network in the United States. The Task Force recommendations reflect a consensus on how to continue and, indeed, improve the diverse activities and responsibilities related to vaccine safety.

The recommendations clearly acknowledge that vaccine safety depends on a complex network of activities and that the modern tools of immunology, molecular biology, and epidemiology can prevent additional diseases through the development of vaccines as well as the assurance of their safety. This report anticipates additional progress in vaccine safety and charts a course to ensure continuation of progress to the benefit of the Nation's children.

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Executive Summary

As we prepare to enter the 21st century, the promise of vaccines has never been greater. If this promise is to be fully realized, vaccines must not only be effective in the prevention of diseases—they must also be safe. Recent reviews by the Institute of Medicine have identified many gaps and limitations, however, in current knowledge of vaccine safety (Howson et al., 1991; Stratton et al., 1994). The Task Force on Safer Childhood Vaccines (TFSCV or the Task Force) was established by the Secretary of Health and Human Services at the direction of Congress, with the sole purpose of examining vaccine safety and making recommendations to the Secretary to ensure development of safer childhood vaccines and improve licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, recall of reactogenic lots or batches, and research on vaccines. This report summarizes the findings and recommendations of the Task Force.

The Task Force comprised representatives from several Public Health Service agencies: National Institutes of Health; Food and Drug Administration; Centers for Disease Control and Prevention; National Vaccine Injury Compensation Program; Office of the General Counsel, Department of Health and Human Services; and National Vaccine Program Office. As with any committee activity, a number of individuals have participated in discussions that resulted in the creation of this report (see acknowledgements).

There are many reasons why examining the safety of childhood vaccines is a critical task and, therefore, mandated by law, but several reasons were emphasized by the Task Force.

The first is a paradox inherent in the very success of vaccines and immunization programs. Concerns about vaccine safety become increasingly prominent when effective use of vaccines in a population reduces the incidence of the target diseases. Yet, since few diseases are eradicable, only immunization programs that maintain public confidence in vaccines can prevent tragic recurrence of disease, as demonstrated by outbreaks of pertussis in several countries during the 1980s. The second reason is that even under conditions of epidemic or endemic transmission, any given individual in the population may escape infection and disease. Vaccination is still essential, however, to protect the population from the spread of disease. Finally, vaccines, unlike therapeutic interventions, are given to healthy individuals. Consequently, the risks associated with any vaccine must be minimal, and vaccines must be extraordinarily safe.

Since 1990, the Public Health Service has created much of the infrastructure necessary to reduce gaps in current knowledge about the safety of vaccines, as identified by the Institute of Medicine, but the process is still incomplete. Safety issues regarding already licensed vaccines have become of paramount importance to the success and stability of immunization programs, vaccine companies, and public support for these activities. At the same time, advances in basic biomedical research and the accelerating pace of the revolution in biotechnology will make a large array of new vaccines possible. The continued improvement and assurance of vaccine safety are as much a research priority as the development of vaccines for the diseases that continue to affect humankind.

Although a number of vaccine-preventable diseases, such as poliomyelitis, may be controlled

and even eliminated globally, others, such as pertussis, tetanus, or diphtheria, are not candidates for eradication. Therefore, vaccination against these diseases must be continued to protect each new cohort of infants, both in the United States and worldwide. The perception of risks due to reports of adverse events will also continue indefinitely. Therefore, systems required to ensure vaccine safety must be maintained. Given new technologies for the development, production, manufacture, regulation, and administration of vaccines, the vaccine safety network for the United States must be enhanced to provide appropriate evaluation of new candidates. To ensure continued public acceptance of vaccines, close monitoring of potential adverse events and adverse reactions, adequate scientific evaluation of hypothesized associations, and appropriate responses to newly identified risks of vaccines, including research and targeted development of new technologies and vaccines, are critical.

The recommendations of the Task Force arise from broad review and evaluation spanning the activities and responsible agencies required to ensure vaccine safety. These recommendations, developed to address gaps and ensure the continuing safety of vaccines, are summarized below:

1. Assess and address national concerns about the risks and benefits of vaccines in order to enhance the education of the public, families, and health care professionals.

As development of vaccines to fight diseases progresses, the assessment of risks and benefits of this intervention has changed, as few health care providers or parents may have seen a case of a vaccine-preventable disease. We need to know more about how to communicate what is known and what is not known about true and perceived risk (Evans et al., 1997). Furthermore, it is extraordinarily difficult to obtain spontaneous report-

ing of adverse events after immunization without a presumption of potential causality. Education must appropriately target the public, families, and health care professionals in order to assure optimal prevention with vaccines. The Task Force made the following recommendations:

- A) Identify the public's and health care professionals' concerns, attitudes, and knowledge about immunization and the benefits and risks of vaccination.
- B) Develop appropriate interventions to enhance knowledge of vaccines and their benefits and risks, reporting of adverse events, and immunization programs and their public health impact.

2. Strengthen the national capability to conduct research and development needed to promote the licensure of safer vaccines.

Vaccine research and development are driven both by scientific advances and by the need to control and prevent disease. Finally, when an effective and safe vaccine is available, the perception or association of true adverse events must be high indeed to support the costly development (approximately \$200 million) of a new vaccine. Technological barriers, however, may confound the process. For example, recombinant hepatitis B vaccines that did not confer the potential risk of transmission of other infections were developed less than a decade after the licensure of serum-derived vaccine. However, the development of safer acellular pertussis vaccines, a complex task that has required new technologies not available 10 years ago, has been a much slower process. To promote the development of safer vaccines, the Task Force made the following recommendations:

- A) Where an association is demonstrated between an adverse event and vaccination,

ensure that these findings will lead to relevant research and vaccine improvements.

- i) Initiate appropriate regulatory review and action.
- ii) Conduct studies of the biologic basis for vaccine adverse events.
- iii) Develop, where feasible, epidemiologic and biologic markers or tests that would be useful to evaluate, predict, or determine risk groups for adverse events.
- iv) Use, wherever possible, vaccines that have been modified or improved to avoid adverse events.

B) Consider new assays to detect potential mediators of adverse events, laboratory correlates of vaccine safety and efficacy, and evaluation of the safety of novel methods to enhance immunogenicity and vaccine delivery technologies and improve the thermostability of vaccines.

C) Foster the active participation of industry and increase public-private collaboration in development of safer vaccines of public health priority.

D) Encourage research and development leading to production of “limited-use vaccines” of potential public health importance through public support of research and development and strengthened interaction with industry. The development of vaccines for limited populations poses special challenges to the development of a safety profile.

3. Strengthen the national capability to conduct surveillance of vaccine-preventable diseases and to evaluate potential adverse events and vaccine efficacy.

Safe use of a vaccine to control disease requires continuous monitoring for the disease as well as for known and potential adverse events following vaccine administration. This type of monitoring makes it possible to answer the following vital public health questions: Is the disease effectively controlled or has something (the vaccine, the human host, or the environment) changed? Has the risk/benefit evaluation altered? Does the use or composition of the vaccine need to be modified in response to different conditions? Are changes in national immunization policies regarding mandated childhood vaccines warranted?

Historically, for both methodological and logistical reasons, effective surveillance for adverse events after licensure has been difficult to maintain. Since 1990, the Public Health Service has initiated major improvements in its ability to conduct both passive and active surveillance for adverse events. Continued support for these projects is critical for adequate monitoring of the present and future safety of vaccines in the United States. To reduce gaps in vaccine surveillance efforts, the Task Force made the following recommendations:

A) Integrate government postlicensure surveillance activities to enhance evaluation of available information, identify gaps, and reduce duplication of effort, with emphasis on the following areas:

- i) Develop new methods and approaches for postlicensure evaluation of the safety and efficacy of vaccines and vaccine uses and ensure that appropriate studies are conducted.
- a) Prospectively evaluate vaccine safety and efficacy in large populations, including adults, to help identify the association of

vaccination with serious but uncommon adverse events. Develop methodology for investigating causality of rare events in vaccine recipients, especially in highly immunized populations.

- b) Develop novel methods and approaches for the detection and evaluation of adverse events associated with new vaccines or new uses of vaccines to supplement systems such as Vaccine Adverse Events Reporting System. Identify and incorporate into the current system other U.S. and international agencies or survey systems that collect information relevant to the evaluation of adverse events.

- ii) Identify differences in rates of adverse events associated with the simultaneous or combined administration of vaccines.

B) Ensure the adequacy of clinical data to support new recommendations for vaccine use, and when appropriate, conduct studies to address safety considerations.

C) Improve the coordination and sharing of data concerning standards, adverse event reports, and analyses with other national control and epidemiologic authorities, including the World Health Organization (regulatory harmonization). The United States should participate in the development of an international network to monitor vaccine safety, taking advantage of the differences and similarities in the vaccines used and in national health care structures.

D) Encourage industry participation in the collection and analysis of data to address

both prelicensure and postlicensure vaccine safety.

- i) Review industry's role and responsibilities in collection, receipt, followup, and analysis of received adverse event reports.
- ii) In consultation with vaccine manufacturers, develop procedures to optimize collection of complete data and analysis of reports by product category, product-specific data by company, and product interaction with other co-administered vaccines.

4. The Task Force recommends that the Interagency Vaccine Group (IAVG), composed of representatives from agencies involved in vaccine research, development, evaluation, regulation, and immunization, be charged with the ongoing responsibility of ensuring that appropriate vaccine safety activities are carried out. The IAVG would be expected to seek routine technical consultation from an expert external advisory body.

The Task Force identified the roles and responsibilities of Federal agencies, vaccine companies, health care providers, the research community, and parents in ensuring that vaccines are safe. Experience over the past century teaches that the activities of each group are linked to the activities of the other groups, making both coordination and communication essential to vaccine safety. Furthermore, the group charged with this responsibility must be able to focus on safety. In accordance with the original mandate to integrate the Nation's vaccine efforts, the National Vaccine Program Office could serve as the secretariat for this group and the entity to ensure action toward emergent vaccine safety needs. The

Task Force defined the IAVG's role as follows:

A) The IAVG would monitor the vaccine safety activities of the various agencies and work to improve interagency communication. It would also facilitate and monitor progress on the investigation and evaluation of reports of serious or frequent adverse events.

- i) Evaluate data relevant to vaccine safety, which may currently be scattered among various agencies and manufacturers.
- ii) Ensure periodic reviews of the safety of licensed vaccines and their recommended immunization schedules. If appropriate, propose studies to address areas where additional data may be informative or supportive, such as in special target groups or programs.
- iii) Ensure effective communication among existing advisory committees

that focus on vaccines and immunization, including specifically the Advisory Commission on Childhood Vaccines, the Advisory Committee on Immunization Practices, the National Vaccine Advisory Committee, and the Vaccines and Related Biological Products Advisory Committee.

B) The IAVG would be expected to seek routine technical consultation from an expert external advisory body.

The Task Force is committed to the concept that the public health is best served by the continued pursuit of safer and more effective vaccines and by the safe use of existing vaccines through improvements in the immunization schedule and delivery of vaccines. The recommendations presented in this report are congruent with the Nation's immunization and vaccine goals presented in the U.S. National Vaccine Plan in 1994.

Introduction

Vaccines and immunization programs have been so remarkably successful in eliminating or controlling many of the more common infectious diseases of childhood that their use is often taken for granted. Their impact is evident every day and everywhere in the United States. Cases of diphtheria, whooping cough (pertussis), tetanus, measles, mumps, and German measles (rubella) are so unusual in the United States that these infections and their consequences are unknown to most Americans. Just a generation ago, the coming of summer brought fears of epidemics of polio; now, iron lungs can be seen only in museums and dusty hospital storerooms. This has been accomplished through the development and use of safe and effective vaccines in national immunization programs around the world. Smallpox was eradicated from the planet in 1977. Polio eradication was defined as a goal for the year 2000. Remarkably, the Americas were declared to be free of wild-virus poliomyelitis on September 29, 1994, with the last recorded case of wild-type disease registered in South America in 1991. Efforts to eradicate polio in Asia and the Pacific are well under way.

The global use of vaccines to control childhood infections has never been broader. The Expanded Programme of Immunization (EPI) of the World Health Organization (WHO) now estimates that 80 percent of the world's children are immunized to protect them against pertussis, diphtheria, tuberculosis, polio, tetanus, and measles. Indeed, vaccines offer solutions to our most common infectious diseases and have become part of the background of everyday life.

Before the development of the vaccines commonly used today, infectious diseases were the most common cause of death, disability, and dis-

ease in the United States. Lives were shortened or devastated by polio, pertussis, measles, and diphtheria (table 1). Severe, life-long complications of these infections were commonplace. Permanent paralysis often followed poliovirus infection. Deafness and blindness were known risks of measles infection. Whooping cough left survivors with permanent brain damage. However, the control over infectious diseases that we now enjoy because of the availability of effective vaccines creates a new and difficult problem. Simply stated, as disease control is firmly established and the infections recede in importance, the adverse events associated with the use of vaccines become more evident and gain in importance; their risk-to-benefit relationship is altered. In 1996, for example, the number of reports to the Vaccine Adverse Event Reporting System (VAERS) was almost double the sum of the reported cases of vaccine-preventable diseases.

Medical interventions and public health measures, including vaccines, are used because they are expected to produce tangible benefits. However, benefits are associated with the risk of **adverse reactions** (caused by the intervention) or **adverse events** (which may or may not be caused by the intervention), perhaps even lethal ones. Many vaccines induce short-lived periods of fever, pain, soreness at the injection site, malaise, or other systemic manifestations. Rarely, more serious reactions may occur. Individuals with unrecognized allergies to eggs, for example, may develop anaphylactic reactions to egg proteins that might be present in some vaccines. Individuals with unrecognized immunodeficiencies may develop serious and perhaps fatal complications when they receive vaccines containing an attenuated living organism (e.g., vaccinia virus in the smallpox vaccine).

or an attenuated poliovirus in the oral polio vaccine). As disease control is established, adverse events or reactions increase in importance. All adverse events must be considered with great care since they may alter the evaluation of risk versus benefit.

Safety is not a condition that can be absolutely guaranteed. As defined in the biologics regulation, safety is “the relative freedom from harmful effect to the persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time” (21 CFR 600.3 (p)).

As a result of the process in place for the development, testing, and licensure of new vaccines,

severe adverse events (those requiring hospitalization, causing chronic medical conditions, or resulting in death) are rare or else would constitute an impediment to vaccine licensure.

Severe adverse events must be considered in relation to the benefit the vaccines produce for both the individual and society. This risk-to-benefit relationship is a more complex one when applied to vaccines than to therapeutic or surgical interventions for many reasons but primarily because of the following:

- ♦ Vaccines are given to persons presumed to be healthy, usually infants and children.
- ♦ Vaccines protect the individual from a statistically predictable exposure to the vaccine-prevented infection, not a current medical problem.¹

Table 1.
Maximum and Current Reported Morbidity Due to Vaccine-Preventable Diseases in the United States

Disease	Maximum Reported Cases	Year Maximum Reported	Reported Cases 1996	Percent Change
Diphtheria	206,939	1921	4	-100.00
Measles	894,134	1941	508	-99.75
Mumps	152,209	1968	751	-99.45
Pertussis	265,269	1934	4,315	-98.37
Polio (wild)	21,269	1952	0	-100.00
Rubella	57,686	1969	238	- 99.96
Congenital rubella syndrome	20,000 (est)	1964-5	2	-99.99
Tetanus	1,560	1948	36	-97.82
<i>Haemophilus influenzae</i> type b invasive disease	20,000	1984	155	-98.65

¹ There are exceptions. For example, bacille Calmette-Guérin (BCG) vaccine is now used in bladder cancer therapy.

- ♦ Vaccines reduce or eliminate the burden of disease in the general population by reducing the spread of disease. Vaccines are sometimes given to a large number of individuals to protect the entire population.
- ♦ Vaccines are often used in campaigns to control epidemic or endemic public health problems; thus, the risk-to-benefit ratio is applied to the general population.
- ♦ Vaccines are often legally required or mandated by States to protect the health of the general population.

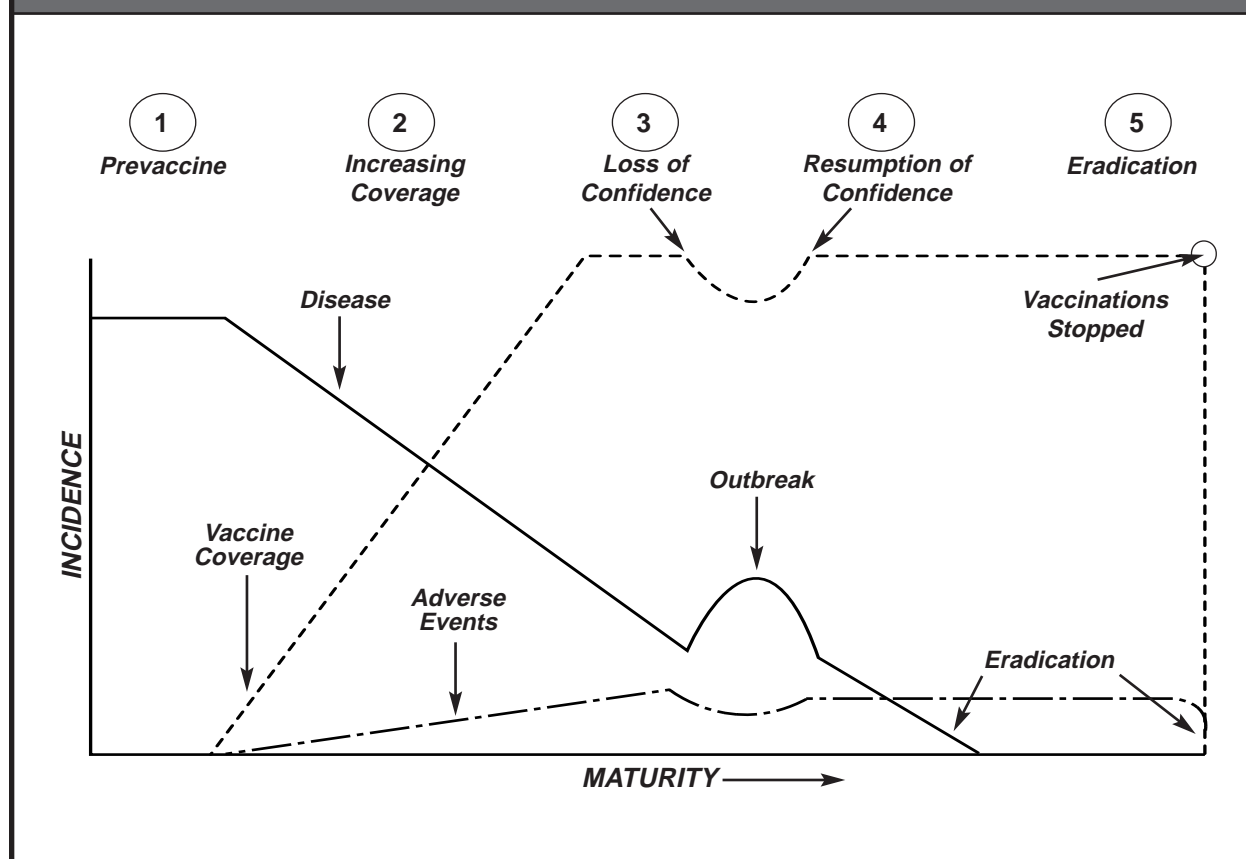
The dynamic nature of the assessment of the benefits and risks associated with any vaccine varies with vaccine coverage, disease incidence, and specific adverse events (Chen, 1994). A few discrete stages, illustrated in figure 1, can be described:

Stage 1: In the prevaccine era, morbidity and mortality due to the disease are high, and for this reason a vaccine is developed.

Stage 2: An effective vaccine results in less disease. With progressive increases in the vaccination levels of the population, immunity in most of the population is derived from vaccination rather than disease. A true vaccine adverse reaction, even if extremely rare, will be observed more “frequently” as the vaccine is used in millions of people.

Stage 3: Over time the threat of the disease will be less urgently perceived, and reports of adverse events will increase (as the vaccine is used in larger populations) and receive greater attention. The public may attribute adverse events to vaccination even though scientific

Figure 1.
Evolution of Immunization Program and Prominence of Vaccine Safety



evidence of causation other than temporal association may be lacking. Such temporal associations are especially difficult to dissect, especially medical events for which etiology remains unknown, such as sudden infant death syndrome (SIDS). This may lead to erosion of confidence in the vaccine, reduction of vaccine usage, and a resurgence of disease.

Stage 4: The cyclical resurgence of disease or the availability of an alternative vaccine may boost public acceptance of vaccination against the disease, resulting in high vaccination levels and reduction of disease. For some vaccine-preventable diseases (e.g., smallpox), epidemiologic characteristics may permit eradication of the causative organism and hence the disease from humankind.

Stage 5: Once eradication is certified, vaccine use can be stopped, thereby eliminating adverse

reactions. For diseases with lower transmissibility or for which effective therapies exist, routine vaccinations may be stopped in some areas before global eradication is confirmed. This occurred with the use of smallpox vaccine in the United States (Henderson and Fenner, 1994). Similarly, the use of oral live attenuated poliovirus vaccine (OPV) has been debated by advisory bodies in the United States, in the face of regional elimination of polio in the Americas.

Although not all of the above stages are applicable to every vaccine (for example, not all diseases are eradicable), this concept of stages illustrates, in a simple way, the dynamic nature of the vaccine-risk tradeoffs and was considered as a framework in the discussions of the Task Force.

Task Force on Safer Childhood Vaccines

The Legal Framework

The Task Force on Safer Childhood Vaccines (TFSCV) was mandated by Congress in 1986 as part of a set of statutes that have fundamentally affected the national childhood immunization system of administration, record-keeping and reporting, compensation for vaccine injuries, labeling, coordination of these responsibilities, and education. Enacted from 1986 through 1989, these statutes have served to initiate or accelerate a number of concurrent activities throughout the Public Health Service (PHS). Appendix 2 details the vaccine legislation from Public Law 99-660, known as the National Childhood Vaccine Injury Act (NCVIA), which enacted Title XXI of the Public Health Service Act in 1986.

NCVIA established the National Vaccine Program (NVP), whose goal is “to achieve optimal prevention of human infectious diseases through immunization and to achieve optimal prevention against adverse reactions to vaccines.” Amendments to the Act in 1987 established the National Vaccine Injury Compensation Program (NVICP) and other required activities. Among them,

- ♦ Section 2125, “Recording and Reporting of Information,” defined the information required to be recorded for the administration of vaccines by every health care provider in the United States.
- ♦ Section 2126 required the Secretary, Department of Health and Human Services (DHHS), to develop vaccine information materials for vaccines subject to the NVICP.
- ♦ Section 2128, “Manufacturer Recordkeeping and Reporting.”

- ♦ Section 2127, “Mandate for Safer Childhood Vaccines,” became effective on December 22, 1987, and required a report on the progress of the issues included in Section 2127(a) (development of safer childhood vaccines; the licensing, manufacturing, processing, testing, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, recall of reactogenic lots, and research on vaccines). Paragraph (b), which calls for the establishment of the Task Force on Safer Childhood Vaccines, was not enacted until December 1989 (Public Law 101-239) (box 1).
- ♦ Section 312 required a review of adverse events associated with pertussis and rubella vaccines.
- ♦ Section 313 required a review of adverse events associated with other childhood vaccines.
- ♦ Section 314 required a review of labeling for warnings, use instructions, and precautionary information.

Reporting Requirements

TFSCV is required to prepare a report and recommendations for the Secretary, DHHS, in consultation with the Advisory Commission on Childhood Vaccines (ACCV), an external advisory group charged with providing advice to the Secretary on the operation of the National Vaccine Injury Compensation Program. The report of the Task Force must include recommendations on how to “promote the development . . . and make or assure improvements” as described in Section 2127(a). In developing the report, the Task Force reviewed the NVICP and found it compatible with the aims of the National Vaccine Plan (U.S. Department of

Health and Human Services, 1994) to ensure the promotion of vaccine safety and effectiveness. This document constitutes the report of the Task Force.

The Task Force Approach

To meet its charge and carry out the reporting requirements under the Act, the TFSCV

(1) reviewed and summarized previously identified safety issues regarding vaccines currently in

use; (2) reviewed current policies and procedures to ensure the safety of vaccines; and (3) determined options for improving existing structures to ensure vaccine safety. As a result of these reviews, the Task Force provided the Secretary with a series of recommendations designed to further enhance vaccine safety.

The Task Force executed this agenda through a series of meetings during which detailed

Box 1. Section 2127(b) of the Public Health Service Act Created the Task Force on Safer Childhood Vaccines.

Section 2127 of the Act embodies explicit language regarding safety as well as the specific mandate of the Task Force on Safer Childhood Vaccines. It provides in its entirety as follows:

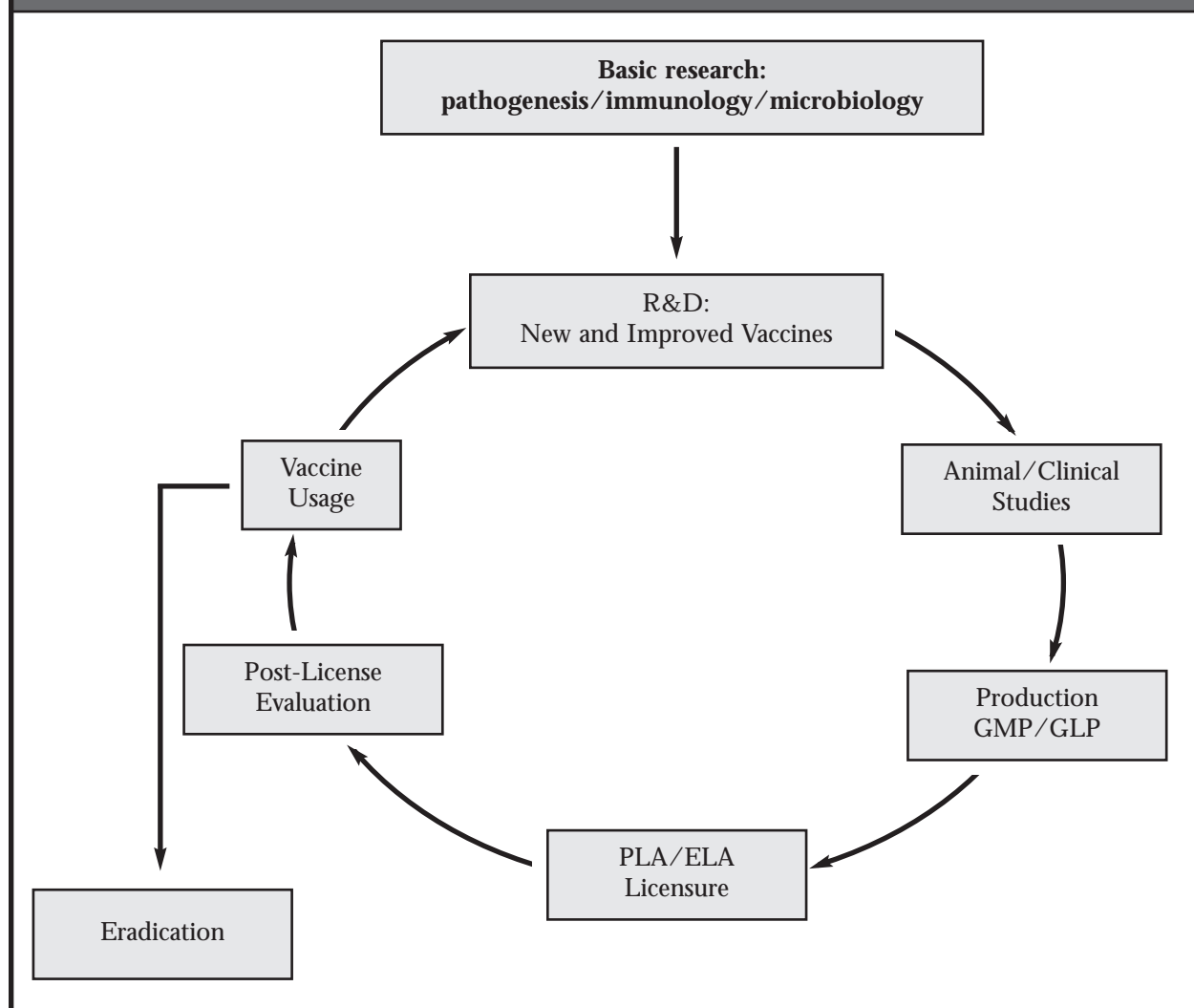
- a. General Rule**—In the administration of this subtitle and other pertinent laws under the jurisdiction of the Secretary, the Secretary shall:
 - (1) promote the development of childhood vaccines that result in fewer and less serious adverse reactions than those vaccines on the market on the effective date of this part and promote the refinement of such vaccines; and
 - (2) make or assure improvements in, and otherwise use the authorities of the Secretary with respect to, the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, and recall of reactogenic lots or batches of vaccines, and research on vaccines, in order to reduce the risks of adverse reactions to vaccines.
- b. Task Force:**
 - (1) The Secretary shall establish a task force on safer childhood vaccines which shall consist of the Director of the National Institutes of Health, the Commissioner of the Food and Drug Administration, and the Director of the Centers for Disease Control.
 - (2) The Director of the National Institutes of Health shall serve as chairman of the task force.
 - (3) In consultation with the Advisory Commission on Childhood Vaccines, the task force shall prepare recommendations to the Secretary concerning implementation of the requirements of subsection (a).
- c. Report**—Within two years after the effective date of this part, and periodically thereafter, the Secretary shall prepare and transmit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate a report describing the actions taken pursuant to subsection (a) during the preceding two-year period.

outlines, position papers, and other documents were used to facilitate discussion. In considering its broad mandate to review vaccine safety and make recommendations, the Task Force examined alternative approaches. Because two comprehensive, congressionally mandated reviews of safety issues for the childhood vaccines were under way by the Institute of Medicine (IOM), cofunded by the National Institute of Allergy and Infectious Diseases (NIAID); the National Vaccine Program Office, Office of the Assistant Secretary for Health; Centers for Disease Control and Prevention (CDC); and Health Resources and Services

Administration (HRSA), detailed examination of vaccine safety issues for each of the licensed vaccines was considered duplicative and not attempted.

The Task Force elected to examine the systems in place to ensure vaccine safety, specifically because of its fundamental premise that assurance of safety of the vaccine supply depends on a sequence of diverse activities that crosscut agency responsibilities as well as the field of vaccinology (figure 2). This continuum of activities includes research through development, testing of experimental vaccines,

Figure 2.
The Vaccine Safety Continuum



production methodology, regulation, surveillance for infectious diseases, establishment of routine criteria for the *in vitro* and animal testing of every lot of vaccine released after licensure (by manufacturers, confirmed by the Food and Drug Administration [FDA]), reevaluation of efficacy and safety following licensure, and the safe use of vaccines in clinical practice. It presents examples of some activities or systems required to ensure the safety of a single vial of vaccine. Furthermore, sites for vaccine safety activities are immensely diverse and include the laboratories of basic researchers and clinical investigators, research laboratories and production suites of vaccine companies, offices of reg-

ulatory agencies, and storage facilities for vaccine in each immunization clinic.

It is essential to recognize that a number of vaccine safety-related activities took place during the deliberations of the Task Force, reflecting a dynamic field driven by both legislated and programmatic activities resulting from the rapid development of research technologies and vaccines. Because the field is relatively small, the same small group of PHS personnel participated in these activities as necessary. Although not a full compilation, box 2 highlights associated and relevant vaccine safety activities from 1990 to 1995.

Box 2. Vaccine Safety Activities From 1990 to 1995

- ♦ As mandated by Section 312, a study sponsored by PHS was conducted by IOM and resulted in publication of the report on the adverse effects of pertussis and rubella vaccines (Howson et al., 1991).
- ♦ As required under Section 313, a second study was undertaken on the adverse effects of the other childhood vaccines (Stratton et al., 1994). Two addenda were requested by PHS to examine research strategies for evaluating vaccine adverse events. Both addenda were published in 1994 (Stratton et al., 1994).
- ♦ An indepth evaluation of vaccine labels and package inserts, as well as one public meeting, was conducted by FDA, as required under Section 314 of the Act. This project continues.
- ♦ The Vaccine Adverse Events Reporting System was implemented by FDA and CDC, and a number of presentations on the design and analysis of this system were presented in 1994 to the Task Force, as well as to the Advisory Commission on Childhood Vaccines, Vaccines and Related Biological Products Advisory Committee, and National Vaccine Advisory Committee. Progress reports to these groups continue.
- ♦ The Vaccine Safety Datalink project, a large linked database, was established by CDC (see Appendix 7) to focus on the study of vaccine safety, utilization, and postlicensure efficacy.
- ♦ Guidelines and reference documents were published by FDA on a variety of safety-related issues, including combination vaccines and their evaluation, and cell lines used in the manufacture of biological products.
- ♦ PHS sponsored scientific workshops addressing issues of vaccine safety, such as:
 - ♦ The Protective and Disease-Enhancing Immune Response to RSV—May 1993 (Anderson and Heilman, 1995)
 - ♦ Combination Vaccines—July 1993 (Williams et al., 1995)
 - ♦ Harmonization of Adverse Event Reporting—September 1993
 - ♦ Meningococcal Vaccine Candidates—February 1994
 - ♦ DNA Vaccines—February 1996 (Smith et al., 1997)
- ♦ Research initiatives specifically targeted to address issues of vaccine safety: Respiratory syncytial virus (RSV)—Request for applications entitled “Mechanism of RSV Vaccine Immunopotentiality” issued by NIAID in FY 1994.
- ♦ Recognition and evaluation of vaccine safety problems: Mumps (non-U.S. strain) vaccine and associated encephalitis in other countries.
- ♦ Investigations of the risk of Guillain-Barré syndrome following influenza immunization by CDC (Tuttle et al., 1997, in press).

Vaccines: Unique Pharmaceuticals

A number of factors serve to differentiate the development, manufacture, and regulation of vaccines from those of other pharmaceutical products. Since vaccines are given to *healthy* infants, children, and adults, acceptable risks for these agents must be minimal indeed to ensure continued public trust and, therefore, maximum acceptance of immunization. Unlike many other pharmaceutical agents, most vaccines are used only a few times in an individual's lifetime, leading to fewer opportunities to examine their impact as well as a much more restricted market. In addition, many vaccines are mandated by the States and are frequently required for school, day care, or employment entry. No other drugs or biologic agents have such widespread mandated use. Vaccination is an integral part of public health practice and well-baby care.

All these factors have led to the evolution of an infrastructure for the delivery of immunization services that focuses primarily on the delivery of vaccines to infants and children. Immunization practices have been developed to make vaccines safe and effective for the child and convenient for the parent.

In many countries, immunization programs and policies are under constant review and revision. In the United States, immunization policies are reviewed by established committees that seek representation from parents, professional societies, State governments, and Federal agencies. Thus, changes in vaccination schedules, such as the addition of newly licensed vaccines to the standard of care, require broad consensus and are relatively slow and more complex than changes in other classes of agents within the pharmaceutical industry. This process has become increasingly complex with the need to

co-administer newly licensed vaccines, often produced by different manufacturers, and ensure their safety and efficacy.

Finally, new vaccines are extensively studied for safety and are unlikely to proceed through lengthy development steps to licensure if there is evidence of severe adverse reactions. After licensure, pediatric vaccines are given to very large numbers of infants at a time when neurologic and other medical conditions are developing, so that some clinical syndromes, however rare and for whatever cause, may occur in temporal association with vaccination. The assessment of safety and of attributable risk is therefore problematic for both new and old vaccines. These and other factors have helped shape the special nature of the vaccine industry at a time of unparalleled growth in the basic sciences and in the technologies for vaccine development.

Public Health and Individual Perspectives on Immunization

In universal immunization programs that aim vaccines at the entire healthy pediatric population, there is an inherent conflict between the interests of the individual and the community (Fine and Clarkson, 1987; Nokes and Anderson, 1991). The tension between individual risks and public benefits is the classic ethical dilemma for public health. For the individual, the goal of immunization is protection from disease. Informed adults are able to weigh benefits derived from this protection against risks associated with the vaccine, particularly for healthy children. In some cases, such as the use of rabies vaccine after exposure to a potentially rabid animal, the risks and benefits are clear and evident. For other vaccines, they are not as obvious. This is especially true if the vaccine to be given protects against a disease

that has become rare due to vaccination or one that is not perceived as a significant threat.

In contrast, the public health interest is the reduction of disease in the community. High rates of immunization may be required to achieve this goal, and for some diseases where there is person-to-person transmission, reducing the incidence by vaccination results in “herd immunity,” with reduction of risk for all community members regardless of their individual immunization status. Where a disease is prevalent and feared, benefits of immunization for the individual far outweigh the risk of disease, in the minds of both the public and the medical community (Freed et al., 1996c). The early years of polio immunization exemplify this situation. If a vaccine is effective, however, and high coverage levels for vaccination are sustained over time, the disease, such as polio, will become rare. In this context, the risks of immunizations may seem to outweigh the benefits from the perspective of the individual, as long as everyone else remains immunized and the risk of transmission of poliovirus remains low. All documented cases of polio in the United States since 1980 have been caused by the live oral polio vaccine. While the numbers have been very small (four to nine cases per year), they represent a risk that may increasingly outweigh the value of oral immunization for some parents and physicians. The change in the risk-to-benefit ratio is heightened by an alternative means of prevention, in this case enhanced inactivated poliovirus vaccine. This change and the selection of the optimal polio immunization policy in the face of elimination of polio from the Americas were discussed at a series of meetings hosted by NVP, IOM, and Advisory Committee on Immunization Practices (ACIP) in 1995.

Herd immunity may be maintained only if the majority of parents accept immunization for their children. When overall population coverage

falls, the pool of susceptible persons increases in size. This situation was demonstrated by the 1989-1990 measles epidemic. While national coverage rates for measles vaccine were acceptable for children to the age of 5, high-risk populations remained unprotected from measles until school age. The population of susceptible children was sufficient to permit sustained transmission of measles virus, producing the largest outbreak of measles since 1977. In 1990 alone, 27,672 cases of measles were reported in the United States. Tragically, the largest annual number of measles deaths (89) since 1971 resulted from this epidemic (NVAC, 1991).

When communities require vaccination for entry into school, day care, or other public settings, some parents may feel that they are being coerced, especially if the procedure is perceived as potentially dangerous or unnecessary. Such was the situation in Sweden when public concerns about both the efficacy and safety of whole-cell pertussis vaccine led to cessation of routine pertussis immunization in 1979 (Gershon, 1990). As a result, pertussis again became an epidemic disease of childhood. A similar situation occurred in Japan, where two deaths after pertussis immunizations led to widespread refusal of the vaccine. The number of cases in Japan then rose from fewer than 1,000 per year in 1975 to 13,105 in 1979, with a case fatality rate of about 1 percent (Gershon, 1990). In the mid-1980s, the American public’s perception of the risks associated with whole-cell pertussis vaccine caused concern for the viability of the immunization program in the United States. In 1985, two manufacturers ceased production of diphtheria, tetanus, and pertussis (DTP) vaccine because of litigation concerns or manufacturing difficulties, leaving a single U.S. manufacturer of the vaccine to supply the needs of the Nation. The price of DTP vaccine increased fivefold in that year and threatened national immunization efforts by making vaccine unaffordable to many programs.

The Dynamic Nature of the Vaccine Field

Advances in basic research fields such as immunology, microbiology, and genetics, together with advances in applied technology, have opened windows of opportunity for the development of new vaccines and the improvement of older ones. These advances have also generated new challenges in vaccine safety as novel classes of immunogens are investigated and new technologies are applied. At the same time, newly emerging pathogens, such as the human immunodeficiency virus (HIV), *Borrelia burgdorferi* (the cause of Lyme disease), and strains of *Mycobacterium tuberculosis* resistant to current antimicrobial agents, present opportunities for vaccine development. In addition, there is a consensus that the development of safe and effective vaccines may be crucial for control of many older infectious diseases. Examples of such conditions include malaria and gonorrhea, both of which continue to be serious public health problems despite the existence of effective treatment.

Changes in health care organization and improvements in computer technology now permit computerized vaccination and medical records to be linked for large numbers of individuals. Compared with passive surveillance systems, such large linked databases (LLDBs) permit a more accurate assessment of the occurrence of serious vaccine reactions and the rates and risk factors that have been identified. The development of regional or even national computerized vaccine registries may one day improve accessibility of an individual's record of vaccines and combinations as well as contraindications to future doses.

The Impact of Basic Research and Technological Advances on Vaccine Safety

The Task Force reviewed examples of research and technological advances in the fields of microbiology, immunology, and chemistry that may have important implications for vaccine safety in the future. For example, detailed molecular

analysis of attenuated live vaccine strains may permit the design of vaccines that are unlikely to revert to virulence. A number of new antigen production systems employing recombinant and chemical conjugation technologies have already resulted in totally new vaccines of known purity or enhanced efficacy (Ada, 1990). The need for easily delivered combination vaccines is fostered by novel technologies for their creation.

However, the use of new technologies for the production and delivery of antigens will present additional challenges to vaccine safety. Some vaccines produced with these technologies are still at the basic research stage while others have been tested in humans. As technologies are developed, safety must remain a priority. Finally, enhancement of the specific immune response to vaccine candidates by immunologic adjuvants is often necessary for new approaches utilizing highly purified antigens. The development and testing of any immunoenhancer are both driven and limited by concerns about its safety in humans.

A summary of the Task Force review of basic research and technological advances and examples of applications of these new technologies are presented in Appendix 3.

New and Emerging Infectious Diseases: Unexpected Challenges to Vaccinology

In the last decade several new or previously unidentified infectious diseases have been recognized as important pathogens and are currently the subject of intensive vaccine research. A brief summary of the development of vaccines for three emerging pathogens—HIV, multidrug-resistant tuberculosis, and Lyme disease—is presented in Appendix 4.

Vaccine Safety Issues Past and Current

Vaccine safety has a long history (for different perspectives, see Freed et al., 1993b; *Money Magazine*, 1996b). Some of the currently recommended childhood vaccines have been in use for decades; they have intensively scrutinized

safety profiles and detailed descriptions of adverse events associated with their use. Others are new agents with which we have relatively few years of clinical experience. A number of vaccines used in the past are no longer licensed in the United States because of safety concerns; appropriately, the memory of these discontinued agents and the problems associated with them persists. Appendix 1 lists childhood vaccines, examples of safety issues associated with their use, and responses to address them. The most recent reviews by the Institute of Medicine (Howson et al., 1991; Stratton et al., 1994), summarized in Appendix 8, examined many conditions for possible causal relationships to vaccines and concluded that most of the conditions in question remained in category 2—that is, the data were insufficient to evaluate.

Laboratory Evaluation of Vaccine

Safety—New Technologies. New technologies, including recombinant DNA or plasmid DNA vaccines and plant vaccines, pose challenges and offer novel approaches to *in vitro* evaluation of safety. Rapid evolution of technologies has dramatically changed the ways in which vaccine safety can be assessed. Older vaccines, developed about 40 years ago, are being reevaluated with these approaches. The new classes of vaccines, including conjugates, recombinants, combinations, and vectored vaccines, will require use of novel biotechnologies and evaluation mechanisms. The current situation is changing rapidly and presents powerful new tools for the evaluation of vaccine safety. A description of these technologies and their potential application to vaccine safety is presented in Appendix 5.

Clinical Evaluation of Vaccine Safety—New Technologies. Tools for the clinical evaluation of vaccine safety that have developed over the past 50 years include clinical trial methodology, biostatistics, and epidemiology, as well as the recent application of molecular epidemiology (Chen, 1994). Thus, it was possible to use viral culture techniques to confirm the hypothesis of

polio-vaccine-associated paralytic poliomyelitis that was based on epidemiologic data. The successful application of molecular epidemiology to enhance surveillance and subsequent vaccine development has been demonstrated in influenza as well as measles.

Evolving Recommendations for Use of Vaccines

As additional information emerges, adjustments and revisions are made to recommendations for the use of vaccines. Examples of new types of data that have caused a change in immunization practice are changes in disease epidemiology and improvements in vaccines that alter target groups for immunization. The Advisory Committee on Immunization Practices of CDC monitors the epidemiology of target diseases and vaccine use and makes recommendations to the Public Health Service on immunization strategies that will ensure public health. Other groups, such as the Committee on Infectious Diseases (“Red Book”) of the American Academy of Pediatrics, the American College of Physicians, and the American Association of Family Physicians, contribute to the evolution of use recommendations, as well as their implementation. The effective dissemination of new immunization recommendations is an important factor in a successful immunization program, especially for the introduction of a new vaccine, and may require approaches that will reach all target audiences: pediatricians, family practitioners, nurses, patients, parents, and policymakers.

Appendix 6 describes examples of immunization recommendations that have evolved over time. They demonstrate that assessments of safety and efficacy are closely linked; that immunization practices must promote both safety and efficacy to protect the public health; and that ensuring both safety and efficacy requires ongoing evaluation of immunization practices. The examples pertain to three diseases and their respective vaccines, namely, measles, pertussis, and hepatitis B.

Current Capability for Assessing Vaccine Safety— Vaccine Evaluation and Licensure

Existing Structures

FDA is the agency responsible for ensuring that only vaccines demonstrated to be safe and effective are licensed and sold in the United States. The authority to regulate vaccines and other biologics is based in both the Public Health Service Act and the Food, Drug and Cosmetic Act. As a result of this legislation, a variety of safeguards are in place to ensure and maintain the safety of vaccines. CDC also plays a major role in developing appropriate recommendations for vaccine use, under advice from the ACIP, and conducts postmarketing surveillance on vaccine safety and efficacy. Before this framework and its implications for assessing safety are described, it is useful to recall that the definition of safety formally used by FDA is stated in the biologics regulation as “relative freedom from harmful effect”—safety cannot be absolutely guaranteed.

The procedures and processes that are in place evolve as new knowledge is gained. As defined by the relevant Code of Federal Regulations, these procedures include extensive laboratory testing of experimental materials before use in human subjects, the use of ethics review committees to evaluate and monitor such experimental use, extensive evaluation in animal model systems, and rigorous requirements to report and investigate any adverse events associated with use of a vaccine.

Procedures for Testing Vaccine Safety

Laboratory and Animal Studies. Assessment of a vaccine’s safety begins long before any testing in humans. A candidate vaccine must first be tested extensively in animals and in the laboratory. The primary objective of this phase of

the testing is to ascertain whether the candidate vaccine exhibits any reactogenicity or toxicity. These studies are also generally used to gain insight into the product’s immunologic properties. Laboratory assays and animal models have been developed for many infectious diseases and have proven to be extremely useful in characterizing the product before experimental use in human subjects. Modifications in vaccines are often introduced at this stage of development to improve immunogenicity and reduce reactogenicity.

Studies in Human Subjects. Clinical studies in the development of all pharmaceutical products proceed along a logical path that involves three discrete phases prelicensure (see box 3). During vaccine development, these three phases are carefully monitored by FDA using the Investigational New Drug Application (INDA or, more commonly, IND) process.

Review of Protocol by Committees and Regulatory Authorities. After the product has been evaluated in animals, the sponsor of the candidate vaccine may apply for permission to conduct testing in humans. Before testing begins, an application must be submitted to FDA. The application will certify that a properly constituted institutional review board (IRB) has reviewed and approved the proposed study and has found that all appropriate safeguards for human subject protection are in place, including signed informed consent. A summary of the preclinical testing is also submitted. If the proposed clinical study is the first evaluation of a vaccine candidate in humans, it is common practice to restrict the number of subjects to be studied. Additional studies are permitted only

after the initial study is completed and the general safety of the candidate vaccine is confirmed. The test protocol is described in detail and contains the study design and a plan for statistical analysis. Information is included on the product's composition, assays of purity and potency, and method of manufacture. Furthermore, the investigators must provide a statement of their qualifications and experience. If, after reviewing the information, FDA determines that test subjects will not be exposed to any untoward risk, clinical trials may proceed. To ensure continued safeguards, the investigators are required, during the course of the trials, to submit annual reports and notify FDA of any adverse events. FDA has published proposed rules for reporting adverse events concerning drugs and biologicals to provide uniformity and facilitate reporting (*Federal Register*, October 27, 1994). The proposed rules also cover amendments to clinical study design and requirements for IND safety reporting.

The IND system of phased clinical trials has several advantages for safety assessment. First of all, the phased entry of subjects allows only small numbers of people to be exposed to unknown risk; more individuals are exposed as more safety data are collected. Should serious reactions occur, the trial can be suspended until the problem is resolved. The system also allows the characterization of adverse events in terms of dose relationships, age relationships, and drug interactions. Finally, all phases of testing are rigorously monitored by FDA.

Licensure Application. After completion of the trials, if the data indicate that the product is safe and effective, the manufacturer may submit an application to FDA to market the product. For a biological product, such as a vaccine, two license applications are required:

- ◆ The first, a product license application (PLA), includes a description of the manufacturing process, results of the clinical trials

that demonstrate the product to be safe and effective, results of required testing on consistency lots of the product, product specifications, and a copy of the package insert that will accompany the product.

- ◆ The second, an establishment license application (ELA), contains information about the facility used to make the product and data demonstrating that the facility is in compliance with the requirements of 21

Box 3. Phases of Vaccine Clinical Trials

- ◆ Phase 1 trials involve very small numbers of healthy subjects (20 to 80). These studies are used to determine whether the product has any gross toxicity problems and to acquire safety and immunogenicity data on dose-related immune responses.
- ◆ Phase 2 trials use controls and larger numbers of subjects (100 to 200). They are designed to further assess product safety as well as to obtain preliminary information on dosing and efficacy.
- ◆ Phase 3 trials use large numbers of subjects (several hundred to thousands) to confirm safety and effectiveness, define risk-benefit relationships, gather information to be incorporated into the package insert, and support marketing approval. This phase may also be used to collect data concerning lot consistency and the acceptability of manufacturing scale-up operations.
- ◆ Phase 4 trials are conducted postlicensure. They may involve different study designs and numbers of subjects, e.g., case control or large cohort studies. Data may be gathered over a number of years.

CFR 600 and 211. These regulations cover the facility's personnel, quality control, buildings, equipment, containers, records, and distribution procedures to ensure a consistent, safe product.

Using an internal panel of scientific experts, FDA reviews and evaluates the data submitted in these applications, resolves any manufacturing deficiencies, conducts its own testing of the consistency lots, permits its own analysis of the clinical and laboratory data submitted, consults with outside panels of experts as appropriate (the Vaccines and Related Biological Products Advisory Committee [VRBPAC]), reviews the labeling (including the sections containing the precautions, warnings, and contraindications), revises the labeling as needed, and obtains commitments from the manufacturer for certain postapproval safety-related actions. In addition, a prelicensing inspection of the production facility is performed to verify the data submitted in the establishment and product license applications. When FDA is assured that the data are complete and adequate and demonstrate that the product is safe and effective, the product and establishment licenses are issued and the manufacturer may begin distributing the product.

Concurrent with license approval, FDA may seek a manufacturer's agreement to conduct certain postmarketing studies (phase 4) to obtain additional information on the product's risks, benefits, and optimal use. These studies include, but are not limited to, studies assessing schedule of administration, use with other products, and adverse event associations. Phase 4 studies conducted by the manufacturer are reportable to FDA for review.

Assessment of Postlicensure Vaccine Safety.

The primary assessment of vaccine safety occurs during investigative clinical trials. Information from these trials serves as the basis for the initial package insert and label statements.

However, even large phase 3 clinical trials (see box 3) involve a relatively limited number of subjects, are brief, and thus will probably detect only the more common acute adverse reactions. These trials may also be conducted among a healthier and more homogeneous population than the one that ultimately uses the vaccine. Information about rare, delayed, or population-specific adverse reactions can be gathered only after vaccine licensure in a variety of phase 4 studies when the vaccine is used more widely. Assessment of vaccine safety continues after licensure through a variety of activities, including a passive reporting system (VAERS), active surveillance in controlled studies, phase 4 studies, lot release tests, and facility inspections. Postlicensure monitoring of product safety continues at several levels.

1. Lot Release Tests. Each lot of product is routinely tested by the manufacturer, usually for general safety, potency, sterility, purity, and identity. Currently, the manufacturer tests each lot of vaccine with a battery of assays appropriate for each specific vaccine as described in 21 CFR (Parts 600-639) and in relation to other criteria addressed in the relevant document of Points To Consider Test results and sends samples from each lot to FDA. FDA reviews the test results and performs confirmatory testing on the samples as needed. If the data are satisfactory, the manufacturer is authorized to distribute the lot.

2. Facility Inspections. All facilities used in the manufacture of vaccines are inspected at least biannually. During these inspections, experts in good manufacturing practices (GMP) and vaccine research from FDA headquarters and regional offices carefully examine and evaluate compliance with FDA regulations of the physical plant, its production records, behavior of plant personnel, adverse event reports, and any other documents or matters that may indicate the quality of operations at that site.

Any observed violations of regulations are recorded in a formal memo (called an FD483 by FDA). At the end of the inspection each violation is discussed with the management to determine the cause of the infraction and remedial action to be taken and to prevent recurrence of each violation. The United States is blessed with a vaccine industry that has a long history of producing safe and effective vaccines in this highly monitored environment. Although violations are occasionally observed, most are minor (e.g., failure to initial the production log for every step of the manufacturing process) and do not present immediate safety concerns. However, should a potential safety hazard be discovered, FDA can halt production and distribution almost immediately. In addition, in such a circumstance FDA can request a recall, a return of all suspected products to the manufacturer.

3. **Approval for Changes.** Another mechanism used by FDA to maintain control over product safety after licensure is the requirement that all changes in indication or usage for the product, labeling, production methods, key personnel, testing, or quality assurance be submitted to FDA for approval before implementation. Each change is thoroughly evaluated. FDA may require additional testing or validation to satisfy safety concerns before approval is granted.

Examples of major actions in which FDA has participated to ensure product safety are listed in box 4.

Phase 4 Studies. Active and passive surveillance methods, as well as targeted studies, are used to monitor postlicensure product safety. These studies are extremely valuable because a rare reaction (i.e., one that occurs only once in thousands of doses) may not be detected even in large clinical trials performed before licensure. Both active and passive surveillance are

needed, however, for early detection if a potential vaccine safety problem occurs. This is a responsibility traditionally shared by CDC and FDA. Historically, CDC has focused primarily on the public sector and safety concerns relevant to ACIP recommendations—serving as the point of contact for health departments and the public—while FDA has focused on the private sector, manufacturers, and regulatory issues. Examples of investigations of vaccine safety conducted by the CDC are listed in box 5.

- a) **Passive Reporting Systems.** Historically, passive reporting has been the major (and in most countries, the only) postlicensure surveillance conducted for vaccine adverse events. The main goals of such systems are to detect new, previously unreported reactions or changes in rates of known reactions. Because of their national scope, passive reporting systems are frequently the only means available to monitor extremely rare adverse events. Passive reporting systems, such as VAERS, act primarily as signal-generating systems. Trends and clusters can be detected through continuous statistical monitoring of the database.

Examples of vaccine-related safety hazards detected in the past by passive surveillance systems are inadequate inactivation of poliomyelitis vaccine (the Cutter incident) and severe reactions to rabies vaccine produced in human diploid cells. The VAERS is a merger of the CDC Monitoring System for Adverse Events Following Immunization (MSAEFI) and the vaccine reports contained in the FDA Spontaneous Reporting System (SRS) programs, for monitoring adverse events associated with vaccination, implemented by the CDC and the FDA on November 1, 1990. The VAERS provides a central focus for reporting (1) specific adverse events associated with vaccines listed in the Vaccine Injury Table required by Section 2125 of the

Public Health Service Act and (2) any other vaccine adverse events occurring after licensure. VAERS' preaddressed, postage-paid forms are widely distributed via annual mailout to physicians likely to administer vaccines. The system has been useful in identifying new vaccine reactions, such as alopecia after hepatitis B vaccine, and changes in known vaccine-related adverse events. After 5 million doses of DTaP (diphtheria, tetanus, and acellular pertussis) were distributed for use as fourth and fifth

doses, rates of adverse events reported to VAERS were about one-third those of DTP, confirming the greater safety of DTaP found in prelicensure clinical trials. Between January 1, 1991, and December 31, 1994, the VAERS program received more than 45,000 reports. About 40 percent of reports came from manufacturers, 24 percent from private health care providers, and 35 percent from State health departments. Approximately 17 percent of all reports concern serious events resulting

Box 4.
**FDA Reports of Vaccine Safety Problems Recognized
Through FDA Review and Testing Procedures**

1971	The diphtheria component of a lot of DTP failed its detoxification test. The vaccine lot was recalled. No injuries reported.
1974	A lot of DTP was recalled because of a failure to resuspend after mixture (flocculent present). No injuries reported.
1980	Through reporting, the manufacturer learned that its DTP vaccine was producing sterile abscesses. FDA was prepared to halt further release of the vaccine, but no action was necessary because the manufacturer voluntarily withdrew the vaccine from the market.
1989	Equine influenza vaccine was inadvertently placed in vials labeled DTP. The DTP vaccine lot was recalled. No vials containing mislabeled vaccine were believed to have left the manufacturer's facilities. No injuries were reported.
1992	An FDA investigation of a key clinical study being conducted to support the licensure of an acellular pertussis vaccine showed that the primary investigator had failed to obtain proper consent, maintain adequate records, or appropriately monitor the study. Under FDA directive, the problems were corrected, and the investigator was required to sign a consent agreement. FDA maintained strict surveillance over the investigator, and the vaccine licensure process was not undermined.
1992	A manufacturer made manufacturing and facilities changes without submitting a supplement to its product licenses. An FDA inspection of the new, unlicensed facility was conducted. Before any action could be taken, the company voluntarily withdrew its license to manufacture vaccines. There were no imminent safety problems.

in life-threatening illness, hospitalization, permanent disability, or death. Regulations requiring that vaccine manufacturers report all known adverse events to FDA were published in 1994 in the *Federal Register*. Should a threat to safety be identified, FDA has the authority to recall any product from the marketplace.

As in most passive reporting systems, underreporting of events occurs (Rosenthal and Chen, 1995). Even if full reporting were to take place, passive surveillance systems would be limited by reporting bias and the lack of accurate data for the population at large. The greatest shortcoming of passive surveillance is its limitation for drawing conclusions of causal association. Passive surveillance systems lack laboratories for evaluating clinical syndromes and obtain only limited relevant information, making epidemiologic assessment of vaccine causality difficult.

- b) Active Surveillance Studies.** Active surveillance studies can be controlled, targeted, and prospective. They can be used to detect rare, serious events not detected in the limited precensure clinical trials or to validate the signal of a potential adverse event detected by passive reporting. Compared with passive reports, they offer the advantage of rigorous scientific design and allow meaningful conclusions to be drawn from the data. For rare adverse events, which may lack unique laboratory or clinical features, active surveillance studies are the best scientific approach to answering questions of causality. Because they are often large, long term, and costly, relatively few such studies have been done of vaccine safety. In recent years, FDA has obtained commitments from manufacturers to continue surveillance of the use of new products to gain additional safety data. One attractive approach to active

Box 5. Examples of Vaccine Safety Studies Conducted or Funded by CDC

1. Associations between poliomyelitis and inactivated (Nathanson and Langmuir, 1963) and oral polio vaccine (Henderson et al., 1964; Schonberger et al., 1976; Strebel et al., 1992)
2. A cluster of infants with SIDS following DTP vaccination (Bernier et al., 1982; Griffin et al., 1988; Chen et al., 1993)
3. Possible association of Guillain-Barré syndrome (GBS) and influenza vaccine (Schonberger et al., 1979; Safraneck et al., 1991; Chen et al., 1992; Terracciano et al., 1997) or tetanus toxoid (Tuttle et al., 1997)
4. A cluster of abscesses following DTP vaccination (Stetler et al., 1985; Simon et al., 1993)
5. Risk of neurologic illness following DTP (Gale et al., 1994; Walker et al., 1988; Griffin et al., 1990) or measles, mumps, and rubella (MMR) vaccine (Griffin et al., 1991; Chen et al., 1991; Black et al., 1997; Davis et al., 1997)
6. Risk of invasive bacterial disease after DTP vaccine (Griffin et al., 1992)
7. Risk of chronic arthropathy after rubella vaccination (Ray et al., 1997)
8. Safety of acellular pertussis vaccine (Rosenthal et al., 1996)
9. Methodology/new surveillance systems for vaccine safety (Fine and Chen, 1992; Chen et al., 1994, 1997)

surveillance is the use of large linked database systems (LLDBs), in which computer linkages join immunization data to outpatient and inpatient records in large health maintenance organizations (HMOs) or other patient databases. This approach may provide appropriate control groups and facilitate analysis by speeding data collection. CDC explored the use of such LLDBs for smaller studies beginning in the mid-1980s. In 1990, CDC contracted with four HMOs with a total population representing 2 percent of the U.S. population for active surveillance studies of vaccine safety (Appendix 7). Preliminary results indicate that this project will help fill many of the gaps and limitations in knowledge of vaccine safety found by IOM.

- c) **Targeted Studies.** Ad hoc epidemiologic studies are designed and conducted to answer specific questions of vaccine safety, especially very rare outcomes, such as Guillain-Barré syndrome, that cannot be studied effectively using LLDBs. This was done for GBS after the 1990-91 and 1993-94 influenza seasons (Lasky et al., 1997).

Continued Research. Active research programs are the foundation for ongoing vaccine safety assessment. As new products and new processes are developed, basic research programs on immunologic mechanisms must be in place to assess potential safety issues. In the event of an alleged cluster of adverse events, it is essential that investigators, support services, and resources be readily available to conduct a timely product evaluation and epidemiologic study. Public concern about vaccine-associated deaths presents a difficult challenge to public health officials and epidemiologists and clearly requires significant attention.

Advisory Bodies for Vaccine Safety

Vaccine safety oversight resides among a broad group of advisory committees and government groups. Most notable are the DHHS immunization-related advisory committees including the Advisory Commission on Childhood Vaccines, the Immunization Practices Advisory Committee, the Microbiology and Infectious Diseases Review Advisory Committee (MIDRAC) of NIAID, the National Vaccine Advisory Committee (NVAC), and the Vaccines and Related Biological Products Advisory Committee. The Department of Defense (DoD) is advised on vaccine and other issues by the Armed Forces Epidemiological Board (AFEB). Overall coordination of programs involving both broad vaccine issues and vaccine safety is the responsibility of the Vaccine Interagency Group of the National Vaccine Program Office. Although safety is not the main or only focus of these groups, aspects of vaccine safety coordination and oversight exist within all of them.

ACCV advises the Secretary of DHHS on the National Vaccine Injury Compensation Program, which provides compensation for certain vaccine-related injuries or deaths and recommends research related to vaccine injuries. This body advises the Secretary regarding the need for childhood vaccine products that result in fewer significant adverse reactions.

ACIP provides advice to the Secretary, the Assistant Secretary for Health, and the Director, CDC, concerning their responsibilities to assist States and localities in the prevention and control of communicable diseases. In addition, the committee reviews and reports on immunization practices and recommends improvements in the national immunization effort. Most recently, Congress added the selection of vaccines for the Vaccines for Children program to the ACIP mandate.

MIDRAC provides the scientific review of contract proposals and grant applications in microbiology and infectious diseases for NIAID. In this capacity the committee advises on policy, planning, and operational matters related to research, development, and evaluation of programs and projects in these fields.

NVAC advises the Secretary, DHHS, and NVP on a broad spectrum of issues relating to vaccine development, licensure, testing, distribution, and use. Several aspects of its work directly involving safety issues include recommending research priorities and other measures to be taken to enhance the safety and efficacy of vaccines, monitoring research and development activities with regard to new or improved vaccines, and coordinating public and professional information and education activities, including those associated with adverse events and contraindications.

VRBPAC reviews and evaluates for FDA data relating to the safety, effectiveness, and appropriate use of vaccines and related biological products requiring licensure by FDA that are intended for use in the prevention, treatment, or diagnosis of human diseases. The committee also considers the quality and relevance of FDA's research program.

AFEB, DoD's advisory body, advises the Assistant Secretary of Defense and the surgeons general of the military departments on operational programs, policy development, and research programs and on requirements for the prevention of disease and injury and promotion of health. The Subcommittee on Disease Control is tasked to provide the latest scientific evaluations and recommendations concerning immunizations, chemoprophylaxis, and therapy, as well as disease surveillance, prevention, and control.

Overall Federal responsibility for implementation of the NVP and coordination of Federal

immunization activities falls to the IAVG, created in the early 1980s. The need for such interagency cooperation in solving national vaccine problems was first defined during the swine flu epidemic, with the formation of an influenza work group. Early efforts to coordinate Federal vaccine responsibilities led to the formation of the Interagency Group to Monitor Vaccine Development, Production, and Usage in 1980. Upon the formation of the NVP, this group was chaired by the NVP. Representatives of each of the vaccine agencies (Agency for International Development, CDC, DoD, FDA, and the National Institutes of Health [NIH]) make recommendations about vaccine policy and operational issues. Specific responsibilities related to vaccine safety oversight involve monitoring research and development activities for new or improved vaccines and coordinating public and professional information and education activities involving vaccine recommendations, adverse events, and contraindications.

The Committee on Infectious Diseases of the American Academy of Pediatrics formulates and revises guidelines for the prevention and control of infectious diseases in children, published in the *Red Book* (AAP, 1994). These guidelines represent consensus developed by the committee in conjunction with liaison representatives (from CDC, FDA, NIH, Canadian Paediatric Society, and NVP as well as ACIP and others) based on review of the published literature and presentations of additional data from experts.

Inevitably, overlap of vaccine safety responsibilities occurs among these various committees and groups. One such area of perceived overlap is in recommendations for vaccine use. ACIP advises CDC in development of use recommendations for vaccines. *The Red Book* Committee provides use recommendations to pediatricians. VRBPAC makes recommendations that are reflected in licensure decisions and labeling of vaccine products. The various recommendations have at times been inconsistent, creating

confusion for the agencies and health care providers.

The need for harmonization of use recommendations within the United States has intensified. The recent licensure of acellular pertussis vaccine for the fourth and fifth doses highlighted the need to ensure closer coordination of vaccine licensure with the development of vaccine use recommendations and the availability of an adequate supply of the newly available vaccine. There currently exists an informal practice to coordinate impending actions on new and improved vaccines. For example, a CDC/ACIP representative attends VRBPAC meetings, and the FDA is represented at ACIP meetings. Further measures to ensure coordination of impending actions on new and improved vaccines have been discussed and recently reviewed (Halsey and Hall, 1995).

Determination of the need for further vaccine safety research also falls to several committees and groups. MIDRAC evaluates the NIAID research agenda from the broadest perspective, ACCV advises the Secretary regarding the need for safer childhood vaccines, and NVAC monitors research activities related to new or improved vaccines. IAVG identifies gaps in research involving vaccine safety. Where possible, the vaccine agencies address these gaps or devise strategies to do so.

The Complexity of Assessing Vaccine Safety

The development of sensitive and specific methods to assess the safety of existing and new vaccines has proven to be a challenge. Although relatively small-scale, phase 2 and phase 3 studies have been useful in estimating the incidence of minor, common adverse reactions (e.g., local erythema, fever, etc.), the medical community and consumers are most concerned about severe, life-threatening events. While such events are believed to occur at a frequency of less than one per million doses administered,

universal application of these vaccines, particularly during childhood, dictates both the need and obligation to develop better means of detection. Practical barriers exist and will continue to be a challenge, as illustrated by the following examples:

OPV and Reversion to Neurovirulence.

Paralysis following administration of oral poliovirus vaccine is believed to occur at a frequency of approximately 1 case per 2.5 million doses distributed and has constituted the sole form of paralytic poliomyelitis acquired in the United States for the past 15 years (Nkowane et al., 1987). Rapid advances in molecular biology have provided opportunities to learn more about the gene segments of the Sabin strains that may be associated with reversion to neurovirulence. Scientists and public health officials are currently evaluating a molecular biologic assay to replace the current test for neurovirulence. The exclusive use of enhanced potency, inactivated vaccine could theoretically eliminate vaccine-associated paralytic polio (VAPP). Both the ACIP and the AAP recommend an immunization schedule that will increase the use of inactivated poliovirus vaccine.

Difficulty of Conducting Safety Evaluations.

Nearly all childhood vaccines are administered on multiple occasions during the first year of life, a time when rare neurological, immunological, and other disorders may manifest themselves. Vaccination is a nearly universal practice so that controlled evaluations to compare the incidence of such events in vaccinated and unvaccinated children have become increasingly difficult to conduct. Large-scale studies involving thousands or millions of children could theoretically provide large enough comparison groups based on differences in the *timing* of vaccination in relation to these extremely rare clinical disorders. However, lack of definitive case definitions for some of these events, combined with difficulties in controlling for myriad confounding variables, has made these studies

virtually impossible to carry out. The cost of such studies has also been considered prohibitive, particularly in the environment of efforts to reduce spiraling health care costs.

Table 2 illustrates a simplistic approach to determining sample sizes required to answer a question of association or causality for a rare adverse event that occurs in children, with the following assumptions: The condition is assumed to be severe and easily recognized, and the condition may be caused by vaccines as well as other stimuli. If we were to conduct a clinical trial to detect a difference of twice the rate between vaccinated and unvaccinated individuals (power = .80 and $\alpha = 0.025$), then the sample size needed for a simple, randomized clinical trial to demonstrate the difference between vaccinated and unvaccinated when the condition occurred in 1 per 100,000 vaccinated would be approximately 9.5 million subjects. The potential rare and serious adverse events of greatest concern would occur less frequently than 1 per 1,000 children. Furthermore, the

assumptions of an ideal clinical trial are rarely met in real life, especially in the setting of postlicensure surveillance because (1) conditions are not fully diagnosed or similarly expressed in every child, (2) symptoms may not always develop within days or hours of immunization, and (3) children are not randomly assigned to vaccination or nonvaccination groups. For these reasons, other study designs, such as case-control studies, are also used to study very rare outcomes.

Combination Vaccines. Vaccine innovation has been successful when directed toward development of products that include a number of antigens. The most recent examples are the combined DTP-Hib (*Haemophilus influenzae* type b) vaccines. Although simultaneous administration of multiple antigens in a combination vaccine reduces the number of injections and simplifies the immunization schedule, the incidence of common and serious adverse events associated with each antigen becomes extremely difficult to estimate. This problem will become even more evident within the next few years, when combination products containing DTaP, Hib, hepatitis B, and inactivated poliovirus vaccines are likely to become available. Combinations are carefully tested as new products prior to licensure (Arbeter et al., 1986; Brunell et al., 1988). Combination vaccines will simplify the immunization schedule and assure that vaccine components are successfully administered.

Conjugate Vaccines. Prelicensure data available for an entirely new vaccine are based on studies in hundreds or thousands but not hundreds of thousands of children. The existence of an elevated risk for very rare adverse events cannot be ruled out solely with experience in a clinical trial population and before experience in the population at large. The evaluation of safety for a new vaccine administered in infancy can be further complicated by co-administration of a vaccine with other childhood vaccines that

Table 2. Sample Sizes Required for Determining Causality by Frequency of Condition		
Rate of Condition in the Vaccinated (1:1 Control and Vaccinated)	Rate of Condition in the Controls	Total Sample Size Required
1/100	0.5/100	9,348
1/1,000	0.5/1,000	94,000
1/10,000	0.5/10,000	942,071
1/100,000	0.5/100,000	9,421,372

may themselves be reactogenic. The clinical evaluation of co-administered vaccines made by two different manufacturers (e.g., hepatitis B

and DTP) may require testing at sites acceptable to both manufacturers.

Gaps in Current Capability for Assessing Vaccine Safety

The IOM reviews, summarized in Appendix 8, examine 76 medical conditions and the scientific data available to assess possible causal relationships to vaccines (Howson et al., 1991, 1992; Stratton et al., 1994). IOM found that for about two-thirds of these conditions, there was either no evidence bearing on the association, or the evidence was insufficient for acceptance or rejection of a causal relationship. Both IOM reports identified gaps and limitations in current knowledge on vaccine safety and made suggestions on research needs.

The Task Force recognized the following areas and addressed them in their recommendations concerning vaccine information, safe practices for using vaccines, and requirements for scientific and technological improvements. Many of the gaps noted in the IOM report, as well as by the review of the Task Force, were due to intrinsic methodological difficulties in conducting vaccine safety evaluations. Other gaps have been addressed through activities undertaken over the past 4 years.

Vaccine Information

- ◆ Assess effectiveness of the vaccine package inserts.
- ◆ Assess and improve health provider knowledge and patient awareness of immunization risks and benefits.
- ◆ Develop or, where possible, improve educational standards on immunization within curricula of health care professionals.
- ◆ Design vaccine information materials that clearly and effectively communicate instructions on use, precautions, and contraindications so that vaccines will be administered in the safest and most effective manner.

(These are already available as second-generation documents following exhaustive review and revision by CDC.)

- ◆ Improve communication with families and persons affected by vaccine adverse events.
- ◆ Develop programs to enhance the reporting and accuracy of reporting by health care providers of potential adverse events in both public and private health sectors.

Safe Use of Vaccines

- ◆ Assure availability of data on complex schedules, including studies of simultaneous administration and combination vaccines, to ensure development of safe recommendations and immunization practices.
- ◆ Ensure consistency and harmonization of use recommendations among advisory groups in the United States.

Improved Surveillance

- ◆ Develop standardized analyses of VAERS data emphasizing evaluation of data for new vaccines and co-administration of vaccines.
- ◆ Enhance analyses of serious events, specifically deaths reported to VAERS, by exploring its use as a registry of potential rare serious adverse events.
- ◆ Incorporate adverse event recording into developing State or regional immunization tracking systems to permit the rapid and detailed evaluation of adverse events.

Intrinsic Improvements in Vaccines

- ◆ Apply emerging technologies to development of improved safety evaluation tests and new laboratory standards.

- ◆ Conduct review of scientific advances in the field of vaccine adverse event methodology (noting reviews published by IOM [Stratton et al., 1994]).
- ◆ Conduct phase 4 studies using LLDBs and other approaches to monitor and assess vaccine safety, efficacy, and effectiveness postlicensure.

Current Capability for Promoting Development and Making and Ensuring Improvements in Vaccine Safety

Several branches of the Public Health Service have responsibilities and capabilities in the field of vaccine research and development. The FDA Center for Biologics Evaluation and Research (CBER) has played a pivotal role in vaccine research for many years. As their principal mandate, NIH and its member institutes support research, both basic and clinical, that will lead to improvement of the Nation's health. CDC and its National Center for Infectious Diseases and National Immunization Program are also actively involved.

Contributions of Basic and Clinical Research

The NIH is the lead PHS agency for vaccine research, focused on basic and clinical research on candidate vaccines. A number of institutes within NIH, including the National Institute of Allergy and Infectious Diseases, the National Cancer Institute, and the National Institute of Child Health and Human Development (NICHD), support vaccine research. Nationally, other research institutions, vaccine companies, FDA, CDC, DoD, and biotechnology firms conduct or support basic, developmental, and clinical research on vaccines. Participating Federal agencies play a central role in research interactions with vaccine companies, international agencies, private organizations, and academic institutions. In 1981, NIAID founded its Program for the Accelerated Development of Vaccines to focus and enhance research activities leading to new vaccines for important diseases, and to improve existing vaccines. Since the program's inception, 12 new or improved vaccines have become available, and 4 have been added to the recommended childhood immunization schedule. In 1990, NIH intensified efforts to evaluate

acellular pertussis vaccines. NIH works closely with other PHS agencies involved in the Nation's research efforts to improve vaccines and prevent disease.

Definition of Disease Pathogenesis. To develop effective vaccines, it is essential to understand the pathogenic mechanisms by which infectious organisms cause disease in humans. For example, basic research on microbial virulence factors of *Staphylococcus aureus* has identified polysaccharides as key components in the disease mechanisms of this important bacterial pathogen.

Expected Immunologic Response to Natural Disease. Generation of effective vaccines requires understanding of human immune responses to disease-causing agents. Vaccines seek to replicate protective immune responses of natural diseases without producing symptoms or pathology. For new generations of vaccines, especially those relying on mucosal immunity, basic research on immune responses is a priority. An NIH-funded research group began preclinical testing in 1991, focusing on the systematic exploration of the mucosal immune responses generated by a variety of vaccines. NIH also sponsors research on mucosal immunity aimed at creating vaccines for sexually transmitted diseases and on the enteric mucosal response that will be critically important to the development of oral vaccines.

Determination of Serological Correlates of Immunity. Evaluation of the immunogenicity of new vaccines hinges on the ability to identify protective immune responses. Serological correlates of immunity remain unclear for a number of targeted diseases and are a research priority.

NIAID is currently sponsoring an intensive investigation of the serological correlates of immunity against *Bordetella pertussis* as part of the acellular pertussis vaccine initiative.

Identification of Candidate Immunogens.

The evolution of basic sciences and biotechnology has allowed for new classes of vaccines made up of immunogenic proteins and polysaccharides of infectious agents. The first of these to be licensed, the *Haemophilus influenzae* type b conjugate vaccines, have demonstrated the safety and practicality of this approach. Investigators are currently attempting to identify candidate immunogens of a number of organisms, including group B streptococcus and pneumococcus.

Intramural Research Laboratories. In addition to supporting research by awarding grants and contracts, NIH supports intramural research laboratories that focus on vaccine development and play an important role in improving vaccine safety and efficacy. The glycoconjugate technology that allowed the development of the Hib conjugate vaccines was the product of intramural research at NICHD. Intramural scientists have active programs in a number of disease and vaccine areas, including respiratory syncytial virus, rotavirus, malaria, and dengue. Other agencies, such as FDA, DoD, and CDC, also support internal laboratory research.

Workshops To Enhance Communication and Peer Review. The workshop mechanism allows PHS to convene focused scientific meetings on issues relating to vaccine improvement and development. When a number of new acellular vaccines against pertussis were under development, NIH convened a workshop involving principal investigators and sponsors of each of these vaccines to discuss safety issues of these acellular agents. Such gatherings provide an opportunity for researchers to meet, share

results, and have their work informally reviewed by peers.

Extramural Process and Peer Review. NIH stimulates and supports research on vaccine improvement and development through a number of mechanisms. NIH operates extensive extramural programs, including the award of research grants, training grants, and extramural research contracts.

Both solicited and unsolicited proposals are funded through support for investigator-initiated research grants in the areas of immunology, microbiology, and pathogenesis essential to the development of safe and effective vaccines. All extramural grant proposals are peer reviewed by expert panels to ensure the highest standards of science.

NIH training grants help ensure the manpower resources necessary for the Nation's vaccine research agenda. These grants typically support junior investigators for 3 to 5 years. Training grants are also used to sustain and develop research infrastructure and capacity in institutions outside PHS. Training grants, like research grants, are peer reviewed.

Research contracts allow the NIH to target research to answer questions, e.g., the development of animal model systems needed for vaccine research and contracts to evaluate the safety of candidate vaccines in humans. These contracts, because they involve research protocols of candidate vaccines with human subjects, are closely coordinated with FDA and vaccine companies.

The vaccine industry, comprising the major vaccine manufacturers as well as biotechnology companies, sponsors or conducts a significant amount of vaccine research. However, because its results are not always published and its financial records are confidential, the extent of

this commitment can only be estimated. Clearly, it contributes significantly to the development and licensure of new vaccines.

Standards for Human Testing. A number of standards have been developed to guide testing of medical intervention in humans. In the United States, conduct of federally supported or FDA-regulated clinical studies is regulated via legislation that includes, among other safeguards, institutional review boards (IRB), whose mandate is the protection of human subjects from research risks, and the informed consent process. In the United States, an IRB must have at least five members and may be established by the institution or independently. An IRB must review and approve an investigator's protocol and informed consent form before a study may be initiated. In addition, an IRB reviews periodic reports from investigators, including reports of any serious adverse reactions and changes in the clinical trial; investigates aspects of the clinical trial to ensure patient safety; terminates the trial if appropriate; and maintains appropriate records of all correspondence regarding the clinical trial.

Phase 1 and 2 Clinical Trials:

Immunogenicity and Safety. The phases of clinical vaccine research in humans have been described earlier (see box 3). In the 1960s, NIAID established the Vaccine and Treatment Evaluation Units (VTEUs) with the capability of conducting clinical trials of candidate vaccines. Currently, NIAID supports seven non-AIDS VTEUs at university-based medical research institutions around the country to accelerate the testing of new and improved vaccines in early human trials of safety, immunogenicity, and protective efficacy. Their experience with vaccine trials, combined with their access to population groups for relevant studies, makes the VTEUs a national resource for early evaluation of vaccines. A number of other clinical centers conduct phase 1 and 2 trials directly sponsored by industry.

Phase 3 Clinical Trials: Efficacy and Safety.

Phase 3 clinical trials are safety and efficacy evaluations that are usually done with large numbers of subjects drawn from the population at risk. PHS has sponsored a number of phase 3 trials of improved or new vaccines, such as the NIH-sponsored acellular pertussis trials performed in Sweden and Italy. Most often, these trials are sponsored directly by industry.

Communication With the Vaccine Research Community.

Communication and coordination among a number of related agencies are essential for an effective immunization and vaccine research and development program. The NIH, individual research groups, IAVG, vaccine companies, international organizations, and government agencies in other countries are important participants in this process. The NIH-sponsored acellular pertussis trial in Italy was a coordinated effort involving the NIH, the Italian Ministry of Health, the Italian Public Health Service, and four private vaccine manufacturers. In addition, the FDA had considerable input in the protocol for the study, the CDC was involved in epidemiologic training of the staff, WHO held an important meeting to discuss the pertussis clinical case definition that would be used in this and other trials, and a number of universities and medical centers in the United States were involved in the phase 1 and 2 trials in which vaccines for the Italian trial were evaluated and selected. Such communication and coordination help ensure that research is based on a true consensus within the world vaccine community and that the results of such a large and expensive trial will be of high order and validity.

Contributions of Manufacturers

In the United States, vaccine companies, in addition to manufacturing the final product, conduct a significant amount of research and vaccine development, provide most of the national expertise in process development for pilot lot production of vaccines, and conduct or

support clinical studies leading to licensure. They are an integral part of the vaccine research and immunization system. Federal agencies, whether regulatory, immunization program, or research-based, work with the vaccine companies to achieve development and safety goals. Improvements in vaccine safety are enhanced by the regulatory framework used by FDA to ensure vaccine safety and efficacy. Field-developed *current* good manufacturing practices (cGMP) are standards that ensure that manufacturers use the best available technology for vaccine production. In FDA's interpretation, the word "current" means that without amendment of the regulations manufacturers will use state-of-the-art technology and procedures. If a health hazard is imminent, FDA has demonstrated capability to recall from the market any questionable vaccine and prevent it from being marketed until the problem is resolved (see box 4). In addition, FDA can require that a manufacturer revise the warnings, precautions, and contraindications in its product literature if a new type of adverse reaction is detected.

Contributions of Surveillance, Vaccine Recommendations, and Epidemiologic Studies

Epidemiology of Disease and Risk Factors.

Understanding the epidemiology and risk factors for any disease is important to its control and prevention and is thus a priority for CDC. This is especially true for a vaccine-preventable disease in order to (1) monitor the impact of vaccines on reducing the target diseases (e.g., Hib) and (2) monitor any changes in disease epidemiology that may require changes in vaccine recommendations (e.g., a two-dose measles vaccination schedule). Such information on disease incidence and risk is critical to overall risk-benefit analysis and to public announcement of recommendations for vaccine use.

Provision of Vaccine to the Public Sector.

As the Nation's largest single purchaser and provider of vaccines, and because vaccines are

critical to its duties in disease prevention, CDC has maintained a major interest in vaccine safety since its founding. A separate Vaccine Safety Activity was created at CDC in 1990 to provide a focus for this important area. Vaccinations not only provide substantial benefit to the individual but also indirectly benefit nonimmune individuals. It is therefore important to ensure that all persons have access to certain vaccinations. Through immunization grants administered by CDC, the public sector has historically been estimated to provide approximately half the childhood vaccines for each birth cohort. This may increase under the Vaccines for Children Program. For special vaccination programs like the National Influenza Program of 1976, the public sector may provide almost all the vaccine.

Risk/Benefit Assessment. ACIP is an advisory group composed of independent experts on immunization and public health. It meets three times annually to weigh the risks and benefits of vaccinations and formulate recommendations for their use by the American public. Accurate and timely information on vaccine safety is critical to ACIP in its deliberations and recommendations.

Warnings/Use Instructions. There is a need for concise and accurate summaries of the risks and benefits of individual vaccines that are understandable to the general public. CDC first developed one-page Important Information Sheets (IIS) for use by all administrators of publicly purchased vaccines in the 1970s. These were updated periodically and aimed at a fifth-grade reading level. The IISs also instructed vaccinees how to report adverse events. In 1988, development of the Vaccine Information Pamphlets mandated by the PHS Act was undertaken by CDC. Simpler sets of Vaccine Information Materials (VIM) were developed, pretested, and released in 1994. VIMs for childhood vaccines are now available.

Distribution/Storage/Stockpile. To ensure the Nation's supply of needed vaccines, CDC negotiates contracts annually with vaccine manufacturers; they agree to store and distribute the vaccine directly to eligible vaccine administrators. Because of the small number of vaccine manufacturers and the need to minimize the risk of vaccine shortages, a system of rotating vaccine stockpiles for the public sector has been established. Safety is served in two ways: The immunization program keeps a stable supply of vaccine, and the required standards (dating, storage, etc.) for maintaining the stockpile are enforced.

Field Surveillance/Adverse Reaction

Reporting. CDC implemented adverse events surveillance in conjunction with the 1976 National Influenza Program. Subsequently, the MSAEFI system was established for the public sector in 1978. Major improvements in MSAEFI were implemented in 1985.

Following the passage of NCVIA, CDC has worked closely with FDA to develop and implement VAERS, a merger of the CDC MSAEFI and FDA SRS databases. CDC serves as the contracting office for VAERS.

Special Ad Hoc Epidemiologic Studies.

Because of its expertise in conducting disease surveillance and epidemiologic studies and its close contact with local health departments that may be the first to learn of potential vaccine safety concerns, CDC has conducted or funded a number of epidemiologic studies to assess potential vaccine safety problems through the years. Examples of such ad hoc studies are listed in box 5. Creation of the LLDB in 1990 has been important in permitting more timely assessment of potential signals generated by VAERS and other sources. CDC has also developed several new methodologies to improve PHS's ability to examine vaccine safety issues, e.g., safety profiles and linkage of MSAEFI reports with pre-vaccine-release lab tests. Other sources of such studies include NIH (the NIH-sponsored epidemiologic study

of SIDS and DTP vaccine) and the U.K. Medical Research Council (National Childhood Encephalopathy Study).

Monitor Vaccine Use. To monitor the national immunization program, CDC compiles a number of types of data on the use of vaccines as indicators of program effectiveness. Such data also generate estimate denominators for VAERS reports used to derive approximate rates for vaccine adverse events. The information includes doses purchased and distributed via the public sector contract, doses administered by age and antigen data, and estimated vaccine coverage via a variety of surveys (e.g., the National Health Information Survey and retrospective school-entry surveys). FDA maintains confidential data on numbers of doses in each vaccine lot distributed for use in the United States.

In the future, State vaccination registries may provide accurate and timely data for use in vaccine safety studies.

Interaction With Global Immunization

Programs. PHS agencies participate in and contribute to global immunization, research, and regulatory programs, by both consultation and collaboration with individual countries as well as participation in multilateral projects. For example, CDC provides substantial technical assistance to various national immunization programs and the WHO Expanded Programme of Immunization. In vaccine safety, CDC staff has assisted WHO and the Pan American Health Organization to develop draft guidelines on vaccine adverse event surveillance. Because an infrastructure for disease surveillance has been developed via the national EPIs, it has been possible to build vaccine adverse event surveillance on an existing framework. CDC staff has also consulted closely with other national EPIs as ad hoc vaccine safety concerns arose (e.g., mumps vaccine aseptic meningitis, allergies to Japanese encephalitis vaccine, and a

cluster of deaths following DTP vaccine). Similarly, FDA is participating in the plans and discussions of international harmonization of adverse event reporting systems so that eventually a database of all safety experience with

vaccines can be easily consulted. NIH has supported trials in high-risk endemic areas and provides scientific expertise and collaborates with the newly formed Global Programme on Vaccines and Immunization.

Experiences Leading to Development of Improved Vaccines

Reports of Adverse Events That Led to Development of New Vaccines

During the past several decades, reports from a number of widely divergent sources have served as the principal driving force behind the development of alternative preparations for existing vaccines. Previously cited examples include the development of acellular pertussis vaccines. Several other examples follow:

Measles—Killed or Live. Although both live attenuated and inactivated measles virus vaccines were licensed in 1963, many providers preferred the inactivated preparation because of the reduced incidence of acute side effects. Within a few years, however, it became apparent that prior receipt of the inactivated vaccine was associated with a relatively severe atypical clinical syndrome when recipients were exposed to natural measles virus infection. Once this problem was recognized, inactivated measles vaccines were no longer recommended. Attention was directed toward development of live vaccines that were further attenuated. Inactivated measles vaccines have not been used since that time, and atypical measles is no longer reported.

Rubella. The early rubella vaccines, first licensed in 1969, included some vaccines produced in dog kidney cells that were associated with a relatively high incidence of arthralgia. The occurrence of these and other systemic reactions (e.g., fever) prompted the development of alternative products grown in duck embryo and later in human diploid cells. This field was recently reviewed, and emphasis was placed on the development of an animal model for arthritis caused by rubella (Frey, 1994).

Influenza. Although inactivated influenza vaccines have been widely used for a number of decades, severe adverse reactions other than anaphylaxis were not described until 1976. At that time, the development and mass application of the so-called “swine” influenza vaccine led to an increasing number of reports of Guillain-Barré syndrome (GBS) within the 30-day period following vaccination. Subsequent investigation confirmed the association of this influenza vaccine with GBS. However, large-scale studies of GBS during the subsequent 3-year period showed no association with influenza antigens other than the swine-like strain. Epidemiologic vigilance continues.

Hepatitis B. The development and licensure of plasma-derived hepatitis B vaccine was heralded as an important event in the prevention of hepatitis B and hepatocellular carcinoma. Unfortunately, plasma donors for vaccine production were often populations at high risk for HIV/AIDS, causing concern about the potential for HIV transmission through vaccination, even though HIV, if present in the plasma, would have been destroyed in the manufacturing process. Nevertheless, the perception of a risk probably reduced hepatitis B immunization rates. An effective, genetically engineered vaccine produced in yeast was subsequently licensed in the United States. As a consequence, the plasma-derived product is no longer available in this country. Although considered to be safe and effective, the plasma-derived product is only used in certain developing countries.

Rabies. Before 1988, the use of preexposure booster doses of human diploid cell rabies vaccine (HDCV) was limited because

approximately 6 percent of recipients who received both primary and booster vaccinations with HDCV developed serum sickness-like reactions. These reactions were believed to be due to the presence of a small amount of human serum albumin that was rendered allergenic by the beta-propiolactone used in making HDCV. To counteract this problem, the Michigan Department of Public Health developed an adsorbed rabies vaccine (licensed in 1988) that did not use human serum albumin as a component in the cell culture medium; consequently, albumin is not present when beta-propiolactone is added to inactivate the virus. Other recombinant approaches are being pursued.

Significant Modifications of Manufacturing Processes

Over the years, FDA has become aware of circumstances that cast doubts on the safety of specific vaccines. In these situations FDA and its predecessor, the Division of Biological Standards (DBS), concentrated their efforts to solve the problems quickly. One example occurred when the work of Sweet and Hilleman indicated that simian virus 40 (SV40) was commonly present in tissue cultures prepared from rhesus monkey kidney cells. This newly recog-

nized agent produced no cytopathogenic changes, which made it very difficult to detect by the safety testing in place at the time.

The publication in March 1961 of the finding that SV40 was relatively resistant to the formalin used to inactivate viruses during manufacture caused great concern. DBS scientists investigated vaccines that were produced in these cultures and discovered several lots containing infectious SV40. Although the virus produced no discernible disease, other DBS personnel demonstrated that volunteers inoculated with a massive dose of the virus developed antibodies and sometimes shed virus in their nasopharyngeal secretions. DBS felt that this evidence, while not extremely alarming, called for action. Taking advantage of the observation that while the virus causes no change in rhesus cells, it regularly did so in the cytoplasm of tissue culture cells prepared from the African green monkey kidney, on May 5, 1961, DBS required that safety testing in green monkey kidney cells be included as part of the battery of regulatory assays. Quick action on DBS's part minimized the number of Americans who might have been exposed to this agent (Meyer et al., 1962). Long-term studies of the potential effects of such exposure are ongoing.

Gaps in Capability for Promoting Development and Making and Ensuring Improvements in Vaccine Safety

Based on this review, the Task Force recognized the following gaps in the U.S. capability to promote development and ensure improvements in vaccine safety.

General Needs

- ◆ Conduct a detailed review of Section 312 and Section 313 congressionally mandated reports conducted and published by IOM, and ensure appropriate response by PHS. Results of these reports are summarized in Appendix 8. The review of the IOM reports is ongoing.
- ◆ Understand host factors associated with adverse reactions to vaccines.
- ◆ Identify microbial properties and mechanisms for adverse events.
- ◆ Determine factors associated with the use of vaccines (licensed as well as IND) in the face of national emergencies (Pandemic Influenza Preparedness Plan, in progress).

Glossary

AAFP	American Academy of Family Practitioners
AAP	American Academy of Pediatrics
ACCV	Advisory Commission on Childhood Vaccines
ACIP	Advisory Committee on Immunization Practices
Adverse Event	Negative sequelae of variable severity that occur after an intervention but may or may not be caused by it
Adverse Reaction	Negative sequelae caused by an intervention: minor (pain, swelling, or low-grade fever), severe (requiring hospitalization), or lethal (causing death)
AFEB	Armed Forces Epidemiological Board
AIDS	Acquired immunodeficiency syndrome
BCG	Bacille Calmette-Guérin (vaccine for tuberculosis)
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
cGMP	Current good manufacturing practices
CVI	Children's Vaccine Initiative
DBS	Division of Biological Standards
DHHS	Department of Health and Human Services
DoD	Department of Defense
DTaP	Diphtheria, tetanus, acellular pertussis (vaccine)
DTP	Diphtheria, tetanus, pertussis (vaccine)
eIPV	Enhanced inactivated poliovirus vaccine
ELA	Establishment license application
EPI	Expanded Programme of Immunization, WHO
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
GLP	Good laboratory practices
GMP	Good manufacturing practices
HbPV	Hib polysaccharide vaccine

HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HDCV	Human diploid cell (rabies) vaccine
HepB	Hepatitis B vaccine
HHE	Hypotonicity, hyporesponsive episode
Hib	<i>Haemophilus influenzae</i> type b
HIV	Human immunodeficiency virus
HMO	Health maintenance organization
HRSA	Health Resources and Services Administration
IAVG	Interagency Vaccine Group of the National Vaccine Program Office
IIS	Important Information Sheet
IL	Interleukin
IND	Investigational new drug
IOM	Institute of Medicine
IPV	Inactivated poliovirus vaccine
IRB	Institutional review board
ISCOM	Immunostimulatory complex
LLDB	Large linked database
MAPS	Multiple-Antigen Peptide Systems
MIDRAC	Microbiology and Infectious Diseases Review Advisory Committee
MMR	Measles, mumps, rubella (vaccine)
MSAEFI	Monitoring System for Adverse Events Following Immunization
NCVIA	National Childhood Vaccine Injury Act
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NVAC	National Vaccine Advisory Committee
NVICP	National Vaccine Injury Compensation Program
NVP	National Vaccine Program
NVPO	National Vaccine Program Office
OPV	Oral poliovirus vaccine

PCR	Polymerase chain reaction
PHS	Public Health Service
PLA	Product license application
PRP	Polyribosylribose phosphate
rDNA	Recombinant DNA
RSV	Respiratory syncytial virus
Safety	“the relative freedom from harmful effect to the persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time” (21 CFR 600.3 (p))
SIDS	Sudden infant death syndrome
SRS	Spontaneous Reporting System
SSPE	Subacute sclerosing panencephalitis
SV40	Simian virus 40
TB	Tuberculosis
Td	Tetanus and diphtheria toxoid, adult type vaccine
Th	Thymus-derived helper lymphocyte
TFSCV	Task Force on Safer Childhood Vaccines (the Task Force)
Vaccine	A preparation that is administered to produce or artificially increase immunity to a particular disease
Vaccine Lot	“that quantity of uniform material identified by the manufacturer as having been thoroughly mixed in a single vessel” (21 CFR 600-639)
VAERS	Vaccine Adverse Events Reporting System
VAPP	Vaccine-associated paralytic polio
VERO	Cell line derived from monkey kidney cells
VIM	Vaccine Information Material
VRBPAC	Vaccines and Related Biological Products Advisory Committee to the FDA
VSD	Vaccine Safety Datalink
VTEU	Vaccine and Treatment Evaluation Unit
VZV	Varicella-zoster vaccine
WHO	World Health Organization

Appendix 1. Examples of Vaccine Safety Issues of Recommended Childhood Vaccines			
Vaccine	Safety Issue	Evidence and Risk Groups	Status
Oral poliovirus vaccine (OPV)	Vaccine-associated paralytic polio (VAPP)	Four to 8 cases/year in the United States or less than one per million doses. Risk is higher after first dose of OPV (1 per 500,000) than for subsequent doses (1 per 2,000,000) (Strebel et al., 1992). More significant in immunocompromised. Mechanism is purported to be reversion of live attenuated vaccine strain to neurovirulence.	Basic research ongoing to define and detect determinants of neurovirulence (FDA, NIH). OPV not to be used in immunocompromised patients or in infants or children who are household contacts of persons with altered immunity. National recommendations to increase use of enhanced inactivated poliovirus vaccine (eIPV) in schedules to decrease risk of VAPP (ACIP, AAP).
	Adventitious agents—simian virus 40 (SV40)	SV40, a viral contaminant of OPV vaccine grown in monkey kidney cell culture, was found to be carcinogenic in hamsters (Eddy, 1961).	Surveillance of population showed no increased incidence of cancer due to SV40 (Mortimer et al., 1981). Long-term studies ongoing. New technologies developed (polymerase chain reaction) to detect adventitious agents. New cell culture production systems developed (OPV grown in VERO cells lines) to obviate need for primary monkey cells.
Inactivated poliovirus vaccine (IPV)	Incomplete inactivation	Cutter incident (1955)—204 vaccine-related cases of polio due to improper production (Nathanson and Langmuir, 1963). In recent history IPV has an excellent safety profile (Stratton et al., 1994).	Strict control over manufacturing standards, consistency, purity, and inactivation. Current regulations include additional filtration systems.
	Anaphylaxis	Neomycin and streptomycin used in manufacture to prevent bacterial contamination. Local reactions in allergic individuals. Theoretical risk.	Surveillance is ongoing.

Appendix 1. continued...

Vaccine	Safety Issue	Evidence and Risk Groups	Status
Diphtheria, tetanus toxoid, pertussis (DTP)	Protracted, inconsolable crying	Causal relation ascribed to cellular pertussis component. Rate is estimated at 0.1 to 6 percent of vaccinated infants (Howson et al., 1991). Typically resolves in under 24 hours.	Seven large-scale acellular pertussis (DTaP) clinical trials in Sweden, Italy, Germany, and Senegal (three sponsored by NIH) showed improved safety profile of acellular vaccines.
	Acute encephalopathy	IOM found evidence "consistent with a causal relation." Studies contradictory: meta-analysis suggests that risk is between 0.0 and 10.5 cases per million doses (Howson et al., 1991).	Acellular pertussis vaccines licensed for infants. Evaluation of VAERS system for reporting adverse neurologic events. Comparison of VAERS and LLDB efficiency of reporting of ongoing febrile seizures (CDC).
	Shock and "unusual shock-like state" — hypotonicity, hyporeponsive episodes	IOM found evidence consistent with a causal relation. Evidence contradictory and rates vary from 3.5 to 291 cases per 100,000 injections.	Comparisons of DTP and DTaP in clinical trials show that HHE is reported more often after whole cell, but can occur after DT and DTaP vaccines.
	Sudden infant death syndrome (SIDS)	All studies reviewed by IOM have suggested either no relationship between SIDS and DTP immunization or a decrease in SIDS risk for DTP recipients.	SIDS surveillance and VAERS surveillance continue. National incidence decreases after "Back to Sleep" campaign.
	Anaphylaxis	Causation is not ascribed to any one component. Rate is estimated at 2 per 100,000 doses (Howson et al., 1991).	Basic research in immunopathology.
Measles, mumps, rubella (MMR)	Acute arthropathy and arthritis	IOM found evidence consistent with a causal relation attributed to rubella component. Rate is 13 to 15 percent of adult women and much lower among men, children, and infants.	Epidemiologic studies under way.
	Chronic arthritis	IOM found evidence consistent with a causal relation attributed to rubella component. Not enough data to determine a rate.	Epidemiologic studies to evaluate risks and risk factors are conducted through LLDB with negative findings.
	Anaphylaxis	Has occurred with MMR. The vaccine contains both trace neomycin and trace egg antigens, which are known allergens and immunogens.	MMR vaccine is contraindicated by a history of allergy or anaphylaxis due to neomycin. Egg allergy is a relative contraindication. Recent studies of safe administration (James et al., 1995) in spite of allergy history.

Appendix 1. continued...

Vaccine	Safety Issue	Evidence and Risk Groups	Status
Measles, mumps, rubella (MMR)	Aseptic meningitis	Urabe vaccine mumps strain only: not used in United States.	Vaccine removed from European and other markets. Strain not available in United States.
	Subacute sclerosing panencephalitis (SSPE)	Rare, severe complication of measles disease, questionably of measles vaccine strain. Rates estimated at 0.7 per million doses of vaccine versus 8.5 per million cases of measles (Johnson et al., 1984).	Passive surveillance for SSPE is ongoing. SSPE incidence rates have fallen with widespread use of MMR. 1993 IOM study (Stratton et al., 1994) concluded that evidence was inadequate to accept or reject a causal relation.
Hib Conjugate	Unknown; few serious AEs described	Safety profile for very rare reactions (less than 1 per 100,000 doses) not yet established.	IOM study included evaluation of safety of this vaccine.
	Anaphylaxis	Has been reported in both United States and Finland (1 per 100,000 doses in the Finnish Hib titer trial). Not enough data to determine rate.	Postlicensure surveillance by FDA.
Hepatitis B vaccine	Unknown; few serious adverse reactions described		IOM study (Howson et al., 1991) includes evaluation of safety profile of this vaccine.
	Anaphylaxis	Potential for this reaction.	IOM report (Stratton et al., 1994).
Combination vaccines	Potential for change in efficacy or safety profile in some combination vaccines	Altered immunogenicity has been demonstrated with live attenuated vaccines (MMR-varicella zoster virus). DTP-Hib safety profile.	Development of safe, effective combinations continues. Evaluated by FDA Advisory Committee before licensure.
Tetanus and diphtheria, adult type (Td)	Anaphylaxis	Local reactions are known to occur. Allergic reactions have been reported, data suggest that serious allergic reactions to Td are rare. Anaphylaxis rate in 1985 and 1986 was 6.4 cases per million doses (Plotkin and Mortimer, 1994).	Vaccine is contraindicated in patients with a history of allergic reaction. Surveillance for adverse events is ongoing.

Appendix 2.

National Vaccine Legislation

The Department of Health and Human Services (DHHS) is responsible for a variety of activities related to vaccines. They include supporting, conducting, and promoting research on vaccines; regulating the manufacture and distribution of vaccines; promoting and administering vaccination services; and monitoring impact of immunization programs on disease rates. Most of these activities have been part of the Department's mission for decades, but others have been assigned since the enactment of the National Childhood Vaccine Injury Act of 1986 (Public Law 99-660).

The issue of safety is and has been inherent in the Department's administration of its varied authority related to vaccines. Indeed, safety is one of the statutory requirements for licensure of vaccines, whether under the authority of section 351 of the Public Health Service Act or under other authorities of the Food and Drug Administration. These include the Food, Drug and Cosmetic Act, expanded by the Durham-Humphrey Amendments of 1951, the Kefauver-Harris Amendments of 1962, and the Drug Regulation Reform Act of 1979. Nevertheless, Public Law 99-660 gave additional emphasis to this issue in the context of childhood vaccines.

On March 13, 1985, the House Energy and Commerce Committee convened an oversight hearing on biotechnology and its role in vaccine development. The Congress recognized that vaccines and immunization were critical to public health. They also concluded that progress in research was providing important opportunities to develop new vaccines against many infectious diseases. The previous decade of disease pre-

vention through immunization had been labeled a global revolution in public health. However, vaccines and immunization were troubled by the liability crisis and perceived disarticulation of the vaccine efforts. In 1986, in response to concerns from parent groups, vaccine companies, and the medical and public health communities, Congress established the National Vaccine Program (NVP) and the National Vaccine Injury Compensation Program (NVICP) under Public Law 99-660.

NVICP is a no-fault system to compensate children and their families presumed to have suffered serious adverse reactions to mandated vaccines. By establishing this program, Congress also aimed to reduce the threat of tort liability for vaccine manufacturers and thereby stabilize vaccine supply, and to improve the climate for new vaccine research and development. The program is funded through an excise tax imposed on each dose of vaccine sold in the United States and by an appropriation from general funds to cover injuries that had occurred prior to the enactment of the law.

While some of these goals have been met, others have proved more elusive. The supply of vaccines was stabilized following implementation of the NVICP, albeit at a higher price due in part to the surcharge placed on vaccines to pay for the compensation fund. Hundreds of petitioners have received awards from the trust fund, and lawsuits filed against domestic diphtheria, tetanus, and pertussis (DTP) vaccine manufacturers dropped from a peak of 255 claims in 1986 to fewer than 20 in 1993 (CDC data). Investigational new drug applications for vaccines have more than doubled from 1986 to

1993, possibly reflecting a more attractive commercial outlook for development of new vaccines. In the research arena there has been a very real increase in vaccine development in both public and private sectors, particularly in the development of acellular pertussis vaccines (Jordan Report, 1995).

NVPO was created to coordinate government and nongovernment activities related to immunization and to allocate funds appropriated under the Act to supplement otherwise unavailable resources. The law requires that the Director, NVPO, ensure procurement of safe and effective vaccines. The effective date of the Act was October 1988.

The National Vaccine Advisory Committee (NVAC) was established under Title XXI to serve as a technical advisory group to NVP. NVAC has as its mission those activities that

will promote the use of vaccines, improve vaccines already in use, and enhance the development of new vaccines.

Vaccine safety and availability are of concern to families, manufacturers, and physicians, and the vaccines agencies of the Public Health Service—the Food and Drug Administration, the National Institutes of Health, and the Centers for Disease Control and Prevention—are each involved in different aspects of the regulation, development, evaluation, and delivery of safe vaccines. Certain aspects of vaccine supply and availability, however, are outside the current scope of the Public Health Service. If the number of manufacturers falls, for any reason, the possibility of a vaccine shortage can become a threat to the public health. In 1985, this became a very real possibility when the number of domestic DTP manufacturers fell to one.

Appendix 3.

Impact of Basic Research and Technological Advances on Vaccine Safety

The Task Force reviewed a number of examples of basic research and technology advances that have important implications for vaccine safety. These advances offer not only challenges to the assurance of safety and a significantly expanded scope for vaccine development, but also the potential for production of purer, better characterized, more consistent components and better understood mechanisms of action than the older generation of biologically active, albeit effective, mixtures.

Host Responses to Infection. New information in the field of immunology about host responses to infection and host responses to immunization has raised important questions with regard to vaccine safety. It is now clear, for example, that recipients of the discontinued killed measles vaccine (given in the United States from 1963 to 1967) can suffer from a potentially severe atypical measles syndrome after exposure to wild-type virus or after revaccination with live attenuated virus. This syndrome is thought to be due to a delayed hypersensitivity reaction and may be related to failure of the killed vaccine to induce antibody to the F protein of the measles virus, a recently characterized virulence factor. Monkeys immunized with killed vaccine, then challenged with live measles developed a striking eosinophilia. This research suggests that the killed vaccine enhanced production of type 2 cytokine during atypical measles.

Another recently appreciated host response is immune enhancement. This response may have played a key role in the complications associated

with an early vaccine for respiratory syncytial virus (RSV). In this situation an inactivated RSV preparation appeared to have been safe on administration but caused severe complications in some vaccinated children when they encountered the wild virus. The pathogenesis of immune enhancement is currently under investigation.

Determinants of Virulence. Attenuation, the process by which organisms lose the ability to cause disease, either through serial passage in organisms or cultures, mutagenesis, and selection of auxotrophs, or by cloning of strains with virulence factor genes deleted or inactivated by mutation, is the basis of live attenuated vaccines. Until very recently, the biological basis of attenuation remained a mystery; it was solely an empirical process. Moreover, because attenuation was not fully understood, the biology of reversion to pathogenicity was also unclear. This ambiguity had important implications for safety, because the genetic changes that differentiated the oral poliovirus vaccine (OPV) strain from the wild virus, for example, had not been identified and could only be tested empirically in monkeys. This situation changed with the advent of monoclonal antibodies to viral antigens, oligonucleotide fingerprinting, and genetic sequencing technology, which can measure genetic homology among isolates and detect subtle strain variations in genetic composition. Genetic mechanisms for virulence and attenuation have now been identified for a number of pathogens (Strebel et al., 1992). The genetic basis for the reversion to neurovirulence of some type 3 polio vaccine strains is currently being elucidated. Genetic sequencing

of mutant type 3 vaccine strains has enabled identification of transcription loci essential for viral protein synthesis (Svitkin et al., 1990). Research of this kind may lead to vaccine strains incapable of reversion that could greatly reduce the incidence of vaccine-associated paralytic polio, the only form of polio seen in the United States since 1980.

Antigen Production Systems. New technologies for the production of antigens have had important effects on vaccine safety. Two vaccines most recently added to the recommended immunization schedule for all children—the hepatitis B and Hib vaccines—are both products of the new technologies. The first hepatitis B vaccine was made from pooled hyperimmune human sera, and, while efficacious and considered safe, it was an expensive product with potential supply problems for mass use. In addition, there was public concern about the possibility of adventitious agents, particularly the AIDS virus. There are currently two licensed recombinant (rDNA) hepatitis B vaccines grown in yeast, the first such recombinant vaccines licensed for use in humans. Recombinant technology eliminates the need for human donors and has produced safe vaccines with a potentially unlimited supply. Because the hepatitis antigen is produced in yeast and is dead, there is no potential for hepatitis B infection associated with immunization.

The licensed Hib vaccines are also the product of new production technology. These are conjugate vaccines, utilizing capsular polysaccharide antigens of *Haemophilus influenzae* type b bound to immunogenic proteins such as the outer membrane protein of *Neisseria meningitidis* or diphtheria toxoids. These conjugates are entirely acellular, have no microbial genetic material, and have thus far had very few reports of minor adverse events. Conjugate vaccines are currently under development for a number of other diseases, notably pneumococcal and

meningococcal infections, and also offer potentially promising safety profiles.

Combination Vaccines. One of the goals of the global Children's Vaccine Initiative (CVI) is the development of vaccines that will protect the world's children from a maximum number of diseases with a minimum number of vaccinations. This is not simply a goal for developing countries. While combination vaccines such as MMR and DTP have long been in use, the recent development of new vaccines and the potential for more vaccines in the future have created intense interest in combining antigens. New vaccines have been added to the U.S. universal childhood immunization schedule (Hib and hepatitis B, second varicella), and the incorporation of IPV in lieu of OPV replaces an oral vaccine with an extra injection. There is a consensus among providers that we cannot add many more visits, or many more vaccinations per visit, without overburdening patients, parents, clinics, and the vaccine delivery system. The appeal of combination strategies becomes apparent as we consider the likely future incorporation of vaccines against rotavirus, RSV, and others. Two formulations of a DTP-Hib combination, one combined in the syringe, have been licensed (Watemberg et al., 1991). There is considerable interest in DTaP-based combinations and an MMR-varicella vaccine (MMR-V) (Brunell et al., 1988).

Combination vaccines will raise important challenges for assurance of safety in addition to efficacy. There are, first, safety concerns over unsuspected adverse reactions to each of the components of the new combination vaccines. Both hepatitis B and Hib vaccines, for example, have been given to many thousands of individuals without serious adverse effects, but they were not given to millions prior to licensure, and very rare adverse reactions were a possibility. Potential cross-reactions of antigens, either in the vial or in terms of the immunologic

response, must also be evaluated. There remains a theoretical possibility of altered immune responses to multiple antigens given simultaneously. This was a problem documented early in the development of trivalent oral polio vaccine but subsequently resolved.

From an epidemiologic standpoint, the evaluation of adverse reactions to combination vaccines is complex. The methodology currently available to assess adverse events related to vaccination will need development and refinement. It may prove particularly difficult to link an event to a specific component of a combination vaccine. The same difficulty is likely to complicate the liability issues surrounding vaccine safety as well.

Microcarrier Cultures. Microcarrier cultures are continuous cell line culture systems that allow for the production of recombinant antigens on a large scale. They have been used to produce antigens of the AIDS virus (the gp160 antigen, which is under evaluation as a potential HIV vaccine) in VERO cell lines, and to produce enhanced inactivated polio vaccine, OPV, and rabies vaccine in France (Barrett et al., 1989; Montagnon, 1989). Microcarriers have the potential to greatly simplify production of vaccines. The safety issues raised by this new technology are essentially the same as for vaccines produced in continuous cell lines without microcarrier technology (explained in the section below on cell lines and vaccines).

Vector Delivery Systems. For many diseases the ideal vaccine is a live attenuated derivative of the disease-producing organism that induces strong, long-lasting immune responses without causing disease. Developing such a vaccine is not always possible, however, either because the organisms cannot be cultured in the laboratory or because reliable attenuation cannot be obtained. One strategy to overcome these

obstacles is to use recombinant DNA technology to insert one or more of the pathogen's genes into another organism, which then serves as a vector for expression of these genes in the host. Several vectors have been tested and are in various stages of development as vaccines. Safety issues may well arise with the vector vaccines, principally from the potential for reactogenicity and pathogenicity in the vector organisms.

♦ **Vaccinia.** Vaccinia virus, effectively used as the vaccine to prevent smallpox, has been extensively studied as a vector for other antigens. Because it has a large genome of approximately 200,000 base pairs and many DNA integration sites, it has the potential for expressing multiple antigens. Antigens from influenza virus, hepatitis B, RSV, foot-and-mouth disease, malaria, rabies virus, dengue virus, HIV, and human proteins have been integrated into vaccinia. However, a number of safety issues may complicate the use of vaccinia as a vector. The vaccinia strain used to eradicate smallpox had a serious adverse reaction rate of about 1 in 50,000 doses, a rate that would be unacceptable by current standards. Adverse reactions to vaccinia included eczema vaccinatum, progressive vaccinia, generalized vaccinia, postvaccinal encephalitis, and skin lesions at the vaccination site (Henderson and Fenner, 1994). The vaccine was contraindicated for patients with immune dysfunction and infants with eczema (Moss, 1991). Vaccinia has the potential to produce disseminated disease in immunocompromised individuals, and a case of vaccine-related disease in a patient with HIV infection has been reported (Redfield et al., 1987). Research is now under way to develop strategies to reduce the virulence of vaccinia and other vector viruses through recombinant technology. A recombinant vaccinia strain has been developed that expresses the human lymphokine interleukin-2 (IL-2). It had a protective effect in immunodeficient animals and may be an

important safety advance for vectored vaccines (Andrew et al., 1991). Other lymphokine genes may also be candidates for inclusion in recombinants. Finally, other promising viral vectors lacking the problems inherent in vaccinia, such as canary pox virus, are being pursued.

- ♦ ***Salmonella***. Various *Salmonella* species have been studied for their potential as vaccine vectors. The rationale for this approach stems from the extensive literature on the value of attenuated salmonellae as vaccines. One currently licensed typhoid fever vaccine, Ty21a, is an attenuated strain of *Salmonella typhi*. Because these strains can be administered orally and interact with the gut-associated lymphoid tissue—where they stimulate high levels of immunoglobulin A production as well as cellular immune responses—they have been most actively studied for use as vaccine vectors for diseases requiring strong mucosal immune responses. *Salmonella* recombinant vectors expressing the *Shigella* O antigen, a subunit of the enterotoxin of *Escherichia coli*, and the colonization factor antigen of *Vibrio cholerae* have been tested in humans. These would be potentially bivalent vaccines, offering protection against *S. typhi* as well as the recombinant antigen. Potential safety concerns with these vaccines include the possibility of reversion to virulence of the *Salmonella* strains in the gut and the well-described reactogenicity of the old killed, whole-cell *S. typhi* vaccines. As with vaccinia, recombinant technology may allow for multiple attenuating mutations to be included in vector strains, and this could increase safety and markedly decrease the potential for reversion to virulence.
- ♦ ***Bacille Calmette-Guérin (BCG)***. The only vaccine currently in use to prevent tuberculosis is an attenuated *Mycobacterium bovis*. It is the most widely used vaccine in the world and, along with HBV, is routinely given to infants at birth. A number of BCG strains exist, and while most are similar “sister” strains, others appear to differ. BCG

has also been studied as a potential vaccine vector. Antigens of HIV and of leishmania have been successfully expressed on BCG. The safety of BCG in immunocompromised individuals remains uncertain, however, and cases of disseminated BCG disease in children with leukemia have been reported (Coppes et al., 1992). BCG is currently contraindicated in the United States for children with HIV infection (AAP, 1994). The safety profile of BCG in healthy recipients is also problematic, given the current demand for vaccines with very low incidence of such effects. Estimates of side effects with BCG range from 1 to 10 percent of recipients and include severe or prolonged ulceration at the vaccination site, regional lymphadenitis, and rarely, lupus vulgaris and BCG osteomyelitis. Clearly, recombinant vector vaccines using BCG strains as carriers will have to develop further attenuated lines of these organisms.

- ♦ ***Adenoviruses***. Adenoviruses have also been used as potential vaccine vectors. Vaccine strains currently used in the military to prevent respiratory disease have been genetically engineered to express foreign DNA from respiratory syncytial virus, hepatitis B virus, and HIV. Studies in rats suggest that adenoviruses may be useful for delivering therapeutic gene products to patients suffering from inherited lung disorders such as alpha-1 antitrypsin deficiency and cystic fibrosis.

Continuous Cell Lines To Produce

Antigens. Advances in biotechnology have allowed for the creation of continuous cell lines for the production of vaccine antigens. The VERO cell line, derived from monkey kidney cells, has been extensively studied in this light and is the basis for an inactivated rabies vaccine grown on these cells and currently licensed in France (the purified VERO rabies vaccine [Merieux]). This vaccine is considerably simpler and cheaper to produce than HDCV, the human diploid cell vaccine, and it has demonstrated that VERO cells can produce large amounts of consistent and pure antigen.

Monoclonal Antibodies and Antigenic Purification. The development of monoclonal antibodies has revolutionized the fields of immunology and microbiology. Monoclonal technology allows for the production of highly specific antibodies to an almost limitless array of substances. In terms of antigen purification for vaccines, monoclonal antibodies can be used to detect minute amounts of undesirable protein, genetic material, and adventitious agents, thus offering the potential for major advances in vaccine safety. Monoclonal technology has been developed for use in viral protein purification, in the development of new vaccines for cholera (Sanchez et al., 1990), leprosy (Clark-Curtis et al., 1990), respiratory syncytial virus (Baker et al., 1992), herpes simplex (Erturk et al., 1991), tuberculosis (Rumschlag et al., 1990), malaria (Tolbert and Rupp, 1989), Chagas disease (Segura et al., 1989), *H. influenzae* type b (Green et al., 1991), and certain types of Hodgkin's lymphoma (Pohl et al., 1992).

Recombinant DNA (rDNA) Techniques To Produce or Express Antigens. The application of recombinant DNA technology to vaccine development has led to a new generation of vaccines. The first licensed vaccine based on rDNA technology was the vaccine for hepatitis B, a yeast recombinant. Recombinant technology allows genes from one organism to be inserted into the genome of another. In the case of hepatitis B vaccine, the gene for the hepatitis B surface antigen (HBsAg) is inserted into yeast, which then expresses the gene product, HBsAG, on its surfaces. This antigen, after extraction and purification, serves as the active agent in the vaccine. Many more recombinant vaccines are under development and are used for recombinant "overexpression" systems in which amplification genes are included in the recombinant organisms to facilitate antigen production (Sanchez et al., 1990). Recombinant vaccines have the potential for marked advances

in vaccine safety over either whole-cell or live attenuated vaccines because of greatly increased purity of antigens.

Other Delivery Systems and Routes

Mucosal Vaccination. Immunization by either an inhaled or intranasal route has been investigated for a number of respiratory infections and has been shown to be effective and safe for children to prevent influenza. There is a scientific basis for the concept of stimulating respiratory mucosal immunity to prevent these infections. Using mucosally delivered vaccines, it also has been shown that these vaccines can stimulate systemic immunity, expanding their potential application. Mucosal vaccines are being developed, with particular attention to immune response, safety, consistency of dosing, patient compliance, and costs.

Microencapsulation. Microencapsulation holds promise for the development of slow-release, single-dose immunizations that could be a major advance toward simplifying immunization schedules. However, this technology raises some important safety issues. They include adverse reactions to antigens that might not be removable from the body, sustained inclusion of solvents whose safety in encapsulated forms needs to be demonstrated, and the potential for microencapsulation to lead to immune tolerance of antigens.

The World Health Organization and CVI are evaluating microencapsulated tetanus toxoid vaccines in animal systems. These are single-dose vaccines of microencapsulated antigen formulated such that antigen is released over a period of weeks to months. The tetanus toxoid is encapsulated in microspheres composed of lactic and glycolic acids. A single dose of such a vaccine could potentially provide long-lasting immunity to *Clostridium tetani*. Theoretically, however, if an allergic or anaphylactic reaction occurred in

association with one of these vaccines, and the antigen or solvent could not be removed, sustained or pulse release could potentially lead to prolonged adverse reactions.

Immune tolerance is a theoretical safety issue with microencapsulated antigens and is being studied carefully. If an antigen is released under the correct conditions (release of small amounts over time), the immune system may become tolerant of an antigen rather than resistant to it. Immune tolerance, rather than protecting against disease, could make an individual *more* susceptible.

A number of microencapsulation systems have been tested in animals, and some have been shown to be safe and immunogenic (Moldoveanu et al., 1989). A phase 1 safety and immunogenicity trial of a liposome-based microencapsulated vaccine against malaria evidenced both safety and impressive immunogenicity in humans (Fries et al., 1992a). It remains to be seen how large a role microencapsulation will play in future vaccine development.

Devices. The administration of vaccines, particularly multicomponent vaccines, may sometimes be best accomplished by special devices, such as multichamber syringes and jet injectors. These devices are often used for the multiple inoculation of individuals during an immunization campaign. FDA requires that the device and the biologic product, both as individual components and in combination, be safe and effective prior to approval. This may complicate and slow the evaluation of products using these devices. For example, issues of safety peculiar to multichamber syringes include consistency in mixing the components of the vaccine and consistency in volume delivered. Jet injectors, previously associated with the transmission of infection from patient to patient, have been made safer with modification of the device itself.

Application of Robotic Technologies to Vaccine Production. After years of use and refinement in the auto and semiconductor industries, robotic technology has recently been applied to vaccine production. Robotic technology offers manufacturers the advantages of increased productivity (there are reports of doubled output), consistent technique (i.e., one manufacturer is claiming more than 700,000 consecutive fillings with no break in sterility), and the ability to simultaneously process batches of several products. To ensure safety and efficacy, utilization of such technology by a manufacturer requires extensive validation of the hardware and software.

Enhancement of Immunity: The Development of New Antigens and Approaches

It has been known for many years that the polysaccharide capsules of certain bacteria are important virulence factors in the pathogenesis of disease. Examples of these virulence factors include the Vi antigen of typhoid, the PRP polysaccharide of *H. influenzae*, and the capsular antigens of pneumococcus and meningococcus. It was also known that these antigens, while important in the disease process, were often poor immunogens and evoked especially weak immune responses in children under 24 months of age. A vaccine composed entirely of one such antigen, the PRP polysaccharide of *H. influenzae* type b, though licensed in Finland, proved to be incompletely protective in American trials (Shapiro, 1990).

The immunologic basis for the response to capsular polysaccharide has begun to be understood. These antigens appear to be T cell independent; i.e., they fail to elicit T cell-mediated immunity and thus stimulate immunologic memory. The development of glycoconjugate technology allowed for the linkage of these polysaccharide antigens to more immunogenic proteins. According to the concept of antigen

“conjugates,” by linking protein and polysaccharide antigens, T cell-mediated as well as humoral responses can be elicited. The first generation of these vaccines has now been licensed; all three are conjugate vaccines of the Hib capsular polysaccharide, PRP, with immunogenic proteins such as the diphtheria toxoid or the outer membrane protein of *N. meningitidis*. These vaccines have proven to be remarkably safe and effective and to elicit good immune responses from infants as young as 6 weeks of age. Recent studies indicate that the different Hib conjugate vaccines can be safely and effectively administered in mixed sequential schedules, eliminating one safety concern.

The glycoconjugate approach should be valuable for other bacterial diseases, such as pneumococcal, streptococcal, and meningococcal diseases. A *Pseudomonas aeruginosa* conjugate vaccine has been tested in humans. This vaccine links a polysaccharide antigen and the toxin A antigen of the same organism to create a novel conjugate (Schad et al., 1991). Clinical evaluations have been done on a malaria conjugate vaccine linking an outer membrane antigen of *Plasmodium falciparum* to the *Pseudomonas* toxin A (Fries et al., 1992b), and on an *E. coli* conjugate vaccine consisting of the O polysaccharide of *E. coli* bound to the O-PS toxin of *Cholera vibrio* (Cryz et al., 1991).

In addition to enhancing immunity through stimulation of both humoral- and cell-mediated immune responses, conjugate vaccines may have another advantage in disease prevention. There is evidence that antibody to polysaccharides alone may not cross the placenta and protect the neonate. Glycoconjugates may stimulate production of immunoglobulins that do cross the placenta, presenting the possibility of maternal immunization against such important neonatal pathogens as group B streptococcus (Baker et al., 1988).

Approaches to Enhancing Immunogenicity—Adjuvants

The advent of recombinant DNA technology has stimulated the production and testing of new subunit vaccines designed to be safer and more efficient. Unfortunately, the limited immunogenicity of many of these peptide or subunit candidates has hindered their development as potential vaccines, making critical various strategies to enhance their capacity to elicit a protective immune response while avoiding the production of harmful effects. Ideally, both improved understanding of the mechanisms of immunoenhancement and the increasing number of available experimental approaches should be integral components of rational vaccine design. The process of development of new vaccines, however, is still highly empirical.

Adjuvants are agents that make it easier for an antigen to elicit an immune response. Depot-type adjuvants, such as alum, were originally thought to increase the immunological half-life of the antigen, but their effects may be mediated by cytokine release (Allison, 1992). Novel adjuvants may function by one of the following mechanisms: (1) changing the conformation of the antigen, thereby enhancing the antigen presentation; (2) preventing proteolytic destruction in the stomach, thus allowing the antigen to pass into the intestines intact for presentation to the gut-associated lymphoid system; (3) targeting antigen directly to M cells of the gut to induce mucosal immune responses; (4) targeting macrophages (particulate adjuvants); and (5) inducing the production of various immunomodulatory cytokines, which act directly on thymus-derived helper (Th) lymphocytes to selectively promote specific arms of the immune system.

The traditional approach to vaccine development assumes that a vaccine will stimulate an immune response that is qualitatively and quantitatively similar to that produced by natural

infection and that this will prevent disease when a person is subsequently exposed to the pathogen. Often, however, the immune response after vaccination is far weaker than that measured after disease, and protection can be variable. Adjuvants are substances that can amplify the cell-mediated and humoral immune response to an antigen. The only adjuvant approved for human use in the United States is aluminum salt (aluminum hydroxide or aluminum phosphate), which, when adsorbed to antigen, augments antibody responses to diphtheria and tetanus toxoids and the hepatitis B vaccines. Vaccines containing alum adjuvants, however, cannot be lyophilized or frozen and are not effective with all antigens, particularly subunit vaccines.

The development of alternative conventional vaccine adjuvants is approached empirically by mixing an antigen with the potential adjuvant, which must then be tested in an animal or human to determine effectiveness and safety. Research in this area is focused on a variety of oil-based emulsions that contain biodegradable materials. Candidates include the Syntex formulation, SAF-1 (containing squalene oil, an amino acid derivative of muramyl dipeptide [threonyl-MDP], and nonionic block polymers), the Ciba-Geigy formulations (containing squalene, surfactants, and a fatty acid derivative of muramyl tripeptide [MTPPE]), the Ribi formulation (containing monophosphoryl lipid A and mycobacterial cell walls), and the saponin derivatives, such as the Cambridge Biotech QS21.

The development of new adjuvants has been dominated by concerns regarding safety (Goldenthal et al., 1993). Some adjuvants are in early trials in humans while others are being developed for veterinary vaccines. Some empirically developed adjuvants have been too toxic for use in humans, causing tissue damage at the site of injection and later granulomatous reactions, pyrogenicity, arthritis, and anterior uveitis in animal models. While effective adjuvants can

reduce the amount of foreign proteins introduced in the vaccinee by achieving protection with fewer doses, extensive experience with adverse reactions caused by candidate adjuvants prompts FDA to demand an approach to testing for safety that is even more careful and systematic than that required for a new antigen. Prudently, the preclinical animal safety studies will use the exact antigen-adjuvant combination, routes of administration, injection volume, and formulation intended for clinical use to best demonstrate freedom from untoward events.

Approaches to Enhancing Immunogenicity— Epitope-Based Strategies

Strategies for immunization with only the relevant epitopes have developed as a result of enhanced understanding of the mechanisms for antigen recognition by B and T cells.

Theoretically, these strategies result in an immune response only to the relevant target and offer the potential for avoiding the toxicity associated with the presence of an immune response to other components of the pathogen. The simplest approach is to link B cell and T cell (helper and cytotoxic) epitopes and use these linear polyepitopes as vaccines. In practice, a good humoral immune response may be elicited, but genetic restrictions may limit the ability to respond to these immunogens. How to optimize the arrangement of epitopes and how to present antigens to the immune system in a manner that maintains conformational and functional integrity (either as synthetic peptides or as expressed peptides in vectors such as vaccinia virus) have not yet been determined but are under investigation in a number of laboratories. Although epitope-based approaches stimulate good antibody responses, they do not stimulate potent cellular immunity, especially cytotoxic T cell responses.

Therefore, other approaches are being pursued. One interesting approach is the use of Multiple-Antigen Peptide Systems (MAPS), which

consist of selected T and B cell epitopes that are conjugated to a polylysine core without a carrier protein (Lu et al., 1991). MAPS are structurally defined, contain a quantifiable amount of well-characterized pure antigen, can be administered intraperitoneally, and generate antibodies with high specificity. This approach has been applied to the development of totally synthetic vaccines for hepatitis B virus, malaria, and HIV infection. Genetic fusion of immunogenic peptides with the nontoxic B subunit of cholera toxin functions as an adjuvant for inducing mucosal immune responses. This combination targets the Peyer's patches in the intestine and results in a brisk, sustained immune response to the attached peptide sequence. Nontoxic derivatives of cholera toxin (and the related *E. coli* heat-labile toxin) are also being evaluated.

Approaches to Enhancing Immunogenicity—Particulate Antigens

Liposomes and microspheres can protect antigens from proteolytic destruction in the stomach, allowing antigen to pass into the intestines intact for presentation to gut-associated lymphoid tissue. Different types of liposomes have been tested over the past 20 years.

Immunostimulating reconstituted influenza virosomes, spherical unilamellar vesicles that combine the hemagglutinin membrane glycoprotein of the influenza virus with antigen, have been tested in a hepatitis A vaccine formulation in humans.

A microcapsule consists of an inner reservoir of antigen surrounded by an outer biodegradable polymer wall (most recently lactide-co-glycolide polyesters) that slowly releases antigen in the lymphoid tissue. The technology has been available for 30 years but has only recently been explored with vaccines. The composition and size of microcapsules are varied; they produce high, sustained immune responses to toxoids and viral antigens. Although the microcapsules

consist of the same material used to make resorbable sutures, the possibility of adverse reactions to a slow-release allergen remains a safety concern, albeit a theoretical one at this point. Because microcapsules between 5 μm and 10 μm in diameter are taken up by the Peyer's patches of the gastrointestinal tract, oral administration of microspheres has been shown to elicit immune responses in mice. The effectiveness of this approach will require careful evaluation because, although microcapsules maintain the peptide in the dry state, avoiding the need for a cold chain, the process exposes antigens to organic solvents, thereby decreasing immunogenicity.

Another approach has been to incorporate antigens into solid particles called ISCOMs (immunostimulatory complexes). These structures are generated by mixing antigen with the detergent Quil A. The ISCOM self-assembles into stable 35-nm cage-like structures held together by the hydrophobic interactions among the matrix (Quil A), added lipids, and the antigen. ISCOMs containing viral membrane proteins have been tested in animals and found to stimulate tenfold increases in antibodies compared to controls. When complexed with glycoprotein, ISCOMs may also induce cytotoxic T cell responses, perhaps through the delivery of antigen directly to the cytosol for presentation with MHC class I molecules. Cytosolic antigen delivery by membrane-active adjuvants mimics the antigen presentation that occurs during viral infection or after immunization with live attenuated vaccines.

Protein cochleates, which are stable protein-phospholipid-calcium precipitates, represent novel formulations to enhance the immunogenicity of antigens. The name derives from their unique structure, a rolled-up lipid bilayer maintained by calcium bridges. Membrane proteins or peptides with lipid anchors can be integrated into this lipid bilayer, which, when

rolled up, protects them from intestinal acid and allows them to be slowly taken up by the Peyer's patches. They can thus serve as efficient methods for multiple antigen presentation and stimulate strong circulating and mucosal antibodies that protect against infection upon challenge in the mouse model. This approach is being tested with influenza, parainfluenza, and HIV vaccines.

Cytokines

An emerging area of immunologic enhancement involves the use of cytokines to direct and boost immune responses. CD4⁺ T-helper lymphocytes have been subdivided into two classes depending on the pattern of cytokines they produce, Th1 and Th2 responses. Th1 cells are prominently involved in cell-mediated immunity and produce cytokines such as interleukin-2 (IL-2) and interferon- γ while Th2 cells help antibody production and produce cytokines such as IL-4 and IL-10. In certain chronic infections, such as leishmaniasis or schistosomiasis, whether the predominant immune response is Th1-like or Th2-like determines the severity of disease. In principle, therefore, the ability to manipulate the immune response toward a Th1- or Th2-like response may permit the enhancing of immunologic protection and minimize immunopathology.

IL-12 is a recently characterized cytokine that may play a pivotal role in immunomodulation. The adjuvant activity of IL-12, when given with antigens, has been demonstrated in a leishmania

vaccine in mice. Immunization of BALB/c mice with *Leishmania major* antigens and IL-12 induced leishmania-specific CD4⁺ Th1 cells that conferred protection against *L. major*. Immunization of control animals with antigen alone elicited Th2-type immune responses that were not protective.

Nucleic Acid Vaccines

The injection of relatively simple DNA-containing bacterial plasmids into muscle of mice has been shown to result in expression of genes encoded by the plasmid. These "DNA" or plasmid DNA vaccines appear to be capable of stimulating both humoral- and cell-mediated immune responses. After a single dose of this type of vaccine, IgG antibodies have been shown to increase for 1 to 2 months, and then either remain stable or gradually fall. Furthermore, cellular immunity has been induced, with both effective priming and boosting observed in mice. The duration of the immune response is observed for at least 19 months after injection. Second, the route of administration may be parenteral, mucosal, or via a gene gun that delivers tiny amounts of DNA-coated gold beads. Finally, this strategy results in relevant antigen production in primates without the use of infectious agents. Thus, this approach to vaccine development is relevant to a number of diseases, including HIV, and can be expected to continue to receive intense scrutiny. Evaluation of the safety of this approach will be central to its safe development and testing in humans.

Appendix 4.

New and Emerging Infectious Diseases: Unexpected Challenges to Vaccinology

In the last decade several new or previously unidentified infectious diseases have been recognized as important pathogens. A number of these diseases are currently the subject of intensive vaccine research. The causative agent of Lyme disease, the spirochete *Borrelia burgdorferi*, was identified less than 10 years ago. Lyme disease is now the most common vector-borne disease in the United States, with several highly endemic regions recognized. HIV, the human retrovirus that is the causative agent of AIDS, has now taken the lives of more than 200,000 Americans. The disease was first identified in the United States in 1981 and has since become a global pandemic. Seven outbreaks of multidrug-resistant *Mycobacterium tuberculosis* have occurred in U.S. hospitals and prisons. These antibiotic-resistant tuberculosis (TB) strains are challenging to treat and represent a new and potentially life-threatening occupational hazard for health care workers, correctional facility staff, and staffs of shelters and service agencies for the homeless, as well as an important nosocomial risk for any hospitalized patient.

Each of these three diseases has presented major challenges to vaccine research. The development of a safe and effective vaccine against HIV is now an international effort. HIV is the first human retrovirus for which vaccine development has been attempted. The current candidate HIV vaccines illustrate the application of biomedical advances to vaccine development; they employ transformed cell lines, recombinant antigens and vectors,

ISCOM technology, and monoclonal antibody assays. A number of HIV vaccines have been tested in HIV-infected patients, and a therapeutic role for these vaccines is a potential benefit of HIV vaccine research. Clearly, an important concern with any HIV vaccine is adventitious transmission of the HIV virus. Development of such vaccines is challenged by concerns about lack of efficacy, transmission of the AIDS virus or any part of its genome, and production of high titers of antibody against an immunodominant, nonneutralizing epitope. The public's concern about these issues may be a barrier to the clinical testing of HIV vaccines and their acceptance.

The Lyme disease agent is the first tick-borne spirochete for which intensive vaccine research has been done. Vaccines for Lyme disease have been successfully tested in humans and found to be efficacious, and an animal vaccine has shown protection in mice, one of the principal host species of the organism. Research focused on characterizing the immune response to *B. burgdorferi*, identifying the antigenic determinants of the organism, and understanding the transmission of the disease to humans has been critical to the development of safe and effective vaccines for Lyme disease.

Although there is a vaccine for tuberculosis, the efficacy of BCG (bacille Calmette-Guérin) in adults is uncertain for any indication. Its efficacy in children is controversial but generally agreed to be limited to the prevention of extrapulmonary complications of TB infection such

as tuberculous meningitis or osteomyelitis (CDC, 1988). Clearly, new TB vaccines are an urgent research priority. The BCG vaccine, one of the oldest vaccines in use, contains a live attenuated organism. The new generation of TB vaccines will undoubtedly employ new strategies, and efforts are under way to create safer and more effective acellular, recombinant, and epitope vaccines that will protect against

TB infection while preserving the usefulness of TB skin testing, with which BCG interferes.

The emergence and reemergence of these infectious diseases point to the need for continued epidemiologic and basic research in infectious diseases, as well as the development of vaccines to control and prevent disease in the future.

Appendix 5.

Laboratory Evaluation of Vaccine Safety

Polymerase Chain Reaction (PCR). PCR is a new technology for detecting the presence of genetic material. PCR works on the principle of gene amplification, so that previously undetectable amounts of nucleic acid, if present in a sample, can be chemically amplified and detected. Because of its extreme sensitivity, PCR represents a major improvement in the ability to detect small amounts of nucleic acid that could not have been detected with earlier methods; thus, its application to vaccines may represent an advancement in the assessment of vaccine purity. PCR can be used to rapidly identify, clone, and sequence microbial genes responsible for disease, abilities that may have important applications for vaccine development and safety. The likelihood of adventitious viral agents in vaccines, or of such agents in vaccines grown in tissue culture, could be substantially reduced by the use of PCR. In addition, PCR is able to detect short segments of altered genetic material. With this capability, PCR has been used to detect altered nucleotide sequences in polio vaccine strains that correlated with reversion to neurovirulence. In one experiment, neurovirulent strains that had passed undetected in the intraspinal monkey neurovirulence test were detected by PCR (Chumankov et al., 1991). This finding could be of considerable importance and presents one approach to decreasing the risk of vaccine-associated polio. Interpretation of PCR assays, however, may be difficult and requires careful consideration of false-positive results.

Transgenic Animals. There have long been theoretical and practical challenges to the extrapolation of animal model immune responses to human diseases. In terms of vaccines,

especially for those diseases where animal models are problematic or nonexistent, the evaluation of safety, immunogenicity, and antigenicity has been difficult. The use of transgenic animals and the development of animal models with genetically altered immune systems have improved this situation considerably. Before the development of a transgenic mouse model, the only animal model for evaluating the polio vaccine strain and its potential for reversion to neurovirulence was the intraspinal injection model in monkeys. This monkey model was expensive and, because it did not involve the gut, less than ideally suited to the evaluation of human disease. The transgenic mouse model offers promise of an improved system for the evaluation of this important vaccine safety concern.

Informatics Revolution. The cross-reactivity of vaccine antigens with human proteins has been considered a potential threat to the safety of vaccination. In theory, if vaccines induce antibodies to proteins that have cross-reactivity with human proteins, these induced antibodies could cause immune-related disease states. This concern has been raised in regard to vaccines against *Streptococcus pneumoniae* type 14, group B streptococcus, and *Neisseria meningitidis*. Certain antigens of the type-14 pneumococcus may share epitopes with human red blood cell membranes. Polysaccharide units of group B streptococcus share sugar structures with human glycoproteins (Hayrinen et al., 1989). There is also some evidence of antigenic similarity between the meningococcus and antigens of developing neural tissue (Finne et al., 1983). At present these potential examples of cross-reactivity are all theoretical, and there is little evidence that such antigenic similarities are of

clinical significance. The ability to identify and sequence antigen genes that may cross-react with human proteins could, however, greatly reduce the possibility of autoimmune or immune-complex complications of vaccination. The informatics revolution, which has resulted in powerful computer systems that facilitate multiple comparisons and storage of information, has greatly improved the sensitivity of these investigations and allows comparisons of human and microbial gene sequences, as well as their amino acid and glycoprotein products.

Control of Manufacture and Release.

Improvements in the safety of vaccines in use today have also been the goal of widespread promulgation of standards for good laboratory practices and current good manufacturing practices by the pharmaceutical industry. These

standards have been used to upgrade and standardize the procedures used in the manufacture of all vaccines in the United States. However, although the World Health Organization has issued guidance documents on manufacture and control authorities, consistent high standards are not used worldwide. Manufacturers, working with the Food and Drug Administration, are collaborating with the International Conference on Harmonization to harmonize requirements and establish a higher set of standards for ensuring vaccine safety. Harmonized preclinical testing standards will enable international test data to be used in the FDA review and licensure process, thereby facilitating availability of foreign-manufactured vaccines in the United States, as well as availability of United States-manufactured vaccines globally.

Appendix 6.

Evolving Recommendations for the Use of Vaccines

Measles. A single dose of live measles vaccine was recommended when the measles vaccine was first licensed. In 1963, the recommended age for vaccination was 9 months; in 1965, it was changed to 12 months. In 1976, the recommended age was changed again to 15 months because vaccine efficacy was found to be lower in children vaccinated at 12 to 14 months.

The 1989-1990 measles epidemic in the United States was principally due to failure to immunize children at appropriate ages; this led to low coverage levels, particularly in high-risk groups (National Vaccine Advisory Committee, 1991). However, even before these outbreaks, immunization strategies were being evaluated because of random measles outbreaks, predominantly among school-age children. Studies of the transmission patterns in the United States during the 1985-1986 period described two major types of outbreaks: among preschoolers (26 percent) and among school-age children (67 percent). Investigation of the outbreaks among highly vaccinated school-age children revealed that vaccination between 12 and 14 months was a risk factor for the outbreaks. However, investigation of the preschool outbreaks revealed that national measles elimination strategies were functioning suboptimally because a large number of cases were occurring in unvaccinated, vaccine-eligible children 16 months to 4 years of age. Various policy changes were considered at that time, including a routine two-dose schedule that would be expected to reduce the number of primary vaccine failures and potentially raise immunity levels above 95 percent (Markowitz et al., 1989).

The next series of investigations of measles outbreaks during the 1989-1990 period revealed other important factors to consider in policy changes. Investigations of those outbreaks demonstrated that financial and situational barriers existed to immunization and that opportunities were frequently missed to assess the vaccination status of children when services were delivered for reasons other than well-child care.

An important consequence of the 1985-1986 and 1989-1990 measles epidemics was that the Advisory Committee on Immunization Practices (ACIP) reevaluated current measles dosage and schedule recommendations. The resulting ACIP recommendations called for a routine two-dose schedule, both doses preferably given as combined measles, mumps, and rubella (MMR). The first dose was recommended to be given at 15 months except in measles transmission areas, whose infants were immunized at 12 months. The second dose was recommended at 4 to 6 years except in high-risk geographic areas. A subsequent recommendation required documentation of receipt of two doses after the first birthday or other evidence of measles immunity for individuals in post-high school settings such as college and persons beginning training in the medical field.

One of the findings from the measles investigations was that many practitioners were failing to immunize at appropriate ages due to such false contraindications such as mild respiratory illness. Thus, as another important consequence of the 1989-1990 measles epidemic, the National Vaccine Advisory Committee

recommended standards of immunization practice that set forth true versus false contraindications for administering all mandatory childhood vaccines. Standards for both the private and public sectors were developed by the Centers for Disease Control and Prevention (CDC) in consultation with a diverse group of interested parties and subsequently adopted by the advisory groups. They include standards for ensuring that vaccine is administered safely.

Most recently, ACIP has examined evidence for the decreasing level of antibody in the cohort of young mothers who have obtained protection from vaccine. As a result, the recommended age for administration of the first MMR has been dropped to 12 months.

Pertussis. Work has been ongoing for more than 20 years to identify and purify the antigens of *Bordetella pertussis* that can be incorporated into protective acellular vaccines that are less reactogenic than whole-cell vaccines. Concern about reactogenicity varies widely by countries. Industry enthusiasm for development of a vaccine that would replace an already licensed, effective vaccine required encouragement from the Public Health Service. In the 1987 Swedish trial, acellular pertussis vaccines had been evaluated earlier in infants, and, although clinical vaccine efficacy was considered good, the estimates were not considered superior to those previously obtained for whole-cell vaccine (there was not a concurrent whole-cell arm in this trial). Thus, the data did not result in licensure of acellular pertussis vaccine for infants in the United States or Sweden. In 1991, the immunogenicity and safety of 13 acellular products were compared with those of whole-cell vaccine in a multicenter, randomized, double-blind study of more than 2,400 U.S. infants conducted at six NIAID Vaccine Evaluation and Treatment Units. The trial demonstrated that most of the acellular products were of equal or superior immunogenicity compared to whole-cell vaccine (Decker and Edwards, 1995). Without a serologic cor-

relate of protection, however, immunogenicity data cannot be used for conclusive determination of efficacy.

The phase 3 efficacy trials in Sweden and Italy demonstrated excellent safety and efficacy compared to U.S. whole-cell vaccine in 1995. Once these vaccines were licensed for infants, ACIP recommended them as the preferred pertussis vaccine. This recommendation will remain unless and until acellular pertussis vaccines have been licensed for infants.

None of the clinical trials, however, will have the statistical power to demonstrate an association, should it exist, between acellular pertussis vaccines and serious but rare neurologic adverse events. Therefore, other approaches to determine causality, such as large linked databases, must be used (see Appendix 7).

Hepatitis B. The reported incidence of acute hepatitis B virus (HBV) infection increased 37 percent between 1979 and 1989. The U.S. estimate is that approximately 1.25 million persons with chronic HBV infection are potentially infectious to others. In the past, the recommended strategy for preventing infection had been to vaccinate high-risk groups only. This strategy alone in the United States was insufficient because it was difficult to identify high-risk persons and vaccinate them before infection, and also because many already infected individuals continue to infect others through their lifestyles, behavior, or occupations. Transmission patterns that tend to vary geographically have made the disease very difficult to control.

The failure of past strategies to reduce disease transmission and the resulting increase in incidence of disease prompted the recommendation to vaccinate all infants as part of a routine universal vaccination schedule to promote a comprehensive approach to elimination of disease transmission. Initially, the recommendation for

universal HBV vaccination was not widely distributed to private practitioners; many physicians were not aware of the new recommendations, and others did not agree with the recommendation for immunizing all infants with HBV vaccine (Freed et al., 1993a). Recent CDC initiatives have addressed the education of

both health care professionals and the public, and new vaccine policies address the financial barriers to effective adoption of new immunization recommendations for HBV. Finally, combination vaccines in development will address the perceived deterrent of multiple injections at single visits.

Appendix 7.

Assessing the Causality of Adverse Medical Events Following Vaccination: Large Linked Databases

A person is vaccinated and experiences an adverse medical event in the following days. Did the vaccine cause the adverse event—is it a true reaction? If it happens frequently to a number of people in the few days after immunization with one vaccine, laboratory results define the vaccine as the cause, or if the patient develops a unique clinical syndrome attributable only to the vaccine, this question can be readily evaluated and answered. If the event is extremely rare, however, and frequently occurs in response to other stimuli, then the question is difficult to answer. This is especially important when the “medical event” is life threatening or causes permanent damage, because it will lead both the individual and the public health system to reevaluate the risks and benefits of the vaccine.

The clinical studies required before vaccines are licensed by the FDA demonstrate vaccine safety and efficacy. However, for financial and logistical reasons, phase 3 trials are generally limited to fewer than 10,000 children, commonly several thousand children. It is obvious that these carefully controlled studies will not be able to answer questions of causation for very rare adverse events—on the order of 1 per 100,000 children. In addition, universal immunization programs make it difficult to find people who are similar except for their vaccination status. Because lack of immunization is not random, unvaccinated people are likely to differ in other ways that are related to the outcomes of interest.

The creation of linked systems of information derived from hospital charts, clinic charts, and

immunization records—large linked databases (LLDBs)—are a recent innovation made possible by powerful computers. In 1990, the CDC funded an LLDB called the Vaccine Safety Datalink (VSD) to monitor vaccination and rare adverse reactions. The VSD links computerized records from four large group health plans, creating a database of medical records that includes vaccinations, hospital discharge diagnoses, emergency room visits, other outpatient medical care, and additional ancillary information. The population under active surveillance numbers over 0.6 million and is composed of children during their first 7 years of life. This is roughly 2 percent of the U.S. population in this age range.

Vaccine Safety Datalink

Development of the VSD makes possible the conduct of observational studies in very large populations to help determine plausible associations between vaccines and rare adverse events. The VSD is the first LLDB study in the United States with sufficient population to permit routine study of rare events. Table 3 identifies health outcomes that are being evaluated for association with respective vaccines.

Having identified people with the illness, treatment, or test of interest, VSD links this information with their immunization records, allowing a comparison of the frequency of recent vaccination (e.g., within 7 days) with those of individuals of similar age, gender, and ethnicity without the illness. Another approach compares rates of illness or condition of interest to those of otherwise similar groups that differ only in timing of immunization.

Table 3.
CDC Vaccine Safety Datalink Project Vaccines and
Conditions Whose Associations Are Being Evaluated

Conditions	Vaccines
Neurologic Aseptic meningitis Increased intracranial pressure Encephalitis and encephalopathy Ataxia Seizures and persistent seizure disorders Reye's syndrome Transverse myelitis Guillain-Barré syndrome Cranial nerve disorders Peripheral nerve disorders Hearing loss Polio and acute paralytic syndromes	DTP, OPV, MMR DTP DTP, MMR MMR DTP, MMR DTP DTP, OPV, MMR DTP, O-IPV, MMR, Hib, HbPV DTP DTP, MMR, IPV MMR OPV
Allergic Anaphylaxis Asthma and bronchitis	DTP, O-IPV, MMR, Hib MMR
Hematologic Hemolytic anemia Thrombocytopenia	DTP DTP, MMR
Infectious and Inflammatory Diarrhea Invasive bacterial disease Autoimmune and immune complex diseases Vaccine-preventable diseases	DTP, MMR DTP, Hib, HbPV DTP, MMR DTP, MMR, Hib
Other Infections Myocarditis Pancreatitis Parotitis Arthropathy and arthritis	MMR MMR MMR MMR
Metabolic Hypoglycemia Diabetes	DTP MMR
Other Site abscesses Persistent crying Collapse—hypotonic, hyporesponsive episodes Breath holding Sudden infant and other unexpected deaths Apnea Adverse events	DTP DTP DTP DTP DTP DTP All

The first 15 months of investigation failed to show, with a few exceptions, any associations between studied outcomes and vaccination. Several relatively common outcomes were found to be associated with vaccination, among them seizures with diphtheria, tetanus, and pertussis (DTP) and measles, mumps, and rubella (MMR) vaccines (table 3). Risk of seizure on the same day as DTP vaccination was three times higher among vaccinated children than among those who had not had a documented vaccination within 30 days. Similarly, the relative risks of seizures within 4 to 7 and 8 to 14 days following receipt of MMR were 2.7 and 3.3, respectively.

Many factors suggest that these seizures are related to fevers. These include the tendency of children to have high fevers and febrile seizures, and DTP's ability to cause fever compared to MMR's side effect of mild illnesses. A nested study of conventional medical records is now in progress. The risk of any seizure event, particular types of seizures, and newly diagnosed seizure disorders will be examined for each vaccine independently and for various combinations of simultaneously administered vaccines. Results may improve the safety of vaccines by using fever-controlling medications with certain vaccinations. This practice may reduce the possibility of fevers, fever-associated seizures, and related health sequelae in young children.

Challenges of LLDBs

Despite the size of the LLDB (over 0.6 million children), there are not enough cases of some rare adverse events to be evaluated. For instance, aseptic meningitis cases are rarely documented after receipt of the MMR, oral poliovirus (OPV), *Haemophilus influenzae* type b (Hib), DTP, and hepatitis B (HepB) vaccines. The numbers of cases were so few (fewer than 15 cases for each vaccine) that it is impossible to determine whether the vaccine was associated with aseptic meningitis or whether these cases happened by chance.

Vaccines are almost always co-administered with other needed vaccines, making determination of causation by a given vaccine very difficult. Also, vaccine combinations will vary depending on the needs of the client, preference of the health care provider, and State policies. For instance, of the total 324,500 OPV vaccines provided, only 3,631 were given alone. The rest were given in some combination that may have included DTP, MMR, Hib, and HepB.

VSD is typical of LLDBs in that most of the records being screened were automated for administrative or clinical purposes, and quality may not meet scientific standards. For many reasons, all medical charts must be reviewed by VSD staff. Record reviews have also helped in identifying cases through use of ancillary information.

Future Plans

By October 1995, 800,000 more records were available for evaluation.

By enlarging the LLDB, it will be possible to evaluate some rare adverse events, including aseptic meningitis, thrombocytopenia (decreased

vaccines and their acronyms

Diphtheria, tetanus toxoid, and pertussis vaccine (**DTP**)

Measles, mumps, and rubella live viral vaccine (**MMR**)

Oral poliovirus vaccine (**OPV**) and enhanced inactivated poliovirus vaccine (**eIPV**)

Haemophilus influenzae type b conjugate (**Hib**) and polysaccharide vaccines (**HbPV**)

"All" includes hepatitis B vaccine (**HBV**), varicella vaccine (**trade name VARIVAX**), and others that are included in the childhood vaccination schedule.

clotting cells in blood), seizures, and other neurological outcomes. Other issues to be investigated include the risks of vaccinating children with various illnesses and the implications of simultaneous vaccinations. The latter is particularly important with the introduction of varicella

and other new vaccines. Completion of these projects will require extensive coordination among CDC, FDA, and the investigators involved in managing the LLDB. Results may affect recommendations regarding vaccine schedules, combinations, and policies for new vaccines.

Appendix 8A. Summary of Conclusions From Institute of Medicine Study of Adverse Effects of Pertussis and Rubella Vaccines		
Conclusion	Adverse Event Reviewed	
	DPT Vaccine ¹	RA 27/3 Rubella Vaccine ²
1. No evidence bearing on a causal relation ³	Autism	
2. Evidence insufficient to indicate a causal relation ⁴	Aseptic meningitis Chronic neurologic damage Erythema multiforme or other rash Guillain-Barré syndrome Hemolytic anemia Juvenile diabetes Learning disabilities and attention deficit disorder Peripheral mononeuropathy Thrombocytopenia	Radiculoneuritis and other neuropathies Thrombocytopenia purpura
3. Evidence does not indicate a causal relation ⁵	Infantile spasms Hypsarrhythmia Reye's syndrome Sudden infant death syndrome	
4. Evidence is consistent with a causal relation ⁶	Acute encephalopathy ⁷ Shock and "unusual shock-like state"	Chronic arthritis
5. Evidence indicates a causal relation ⁷	Anaphylaxis Protracted, inconsolable crying	Acute arthritis

Source: Howson, C.P.; Howe, C.J.; Fineberg, H.V., eds. *Adverse Effects of Pertussis and Rubella Vaccines*. Washington, DC: National Academy Press; 1991.

¹ Evidence does not differentiate between DPT vaccine and the pertussis component of DPT vaccine except in the case of protracted, inconsolable crying where the evidence implicates the pertussis component specifically.

² RA 27/3 MMR, Trivalent measles-mumps-rubella vaccine containing the RA 27/3 rubella strain.

³ No category of evidence was found bearing on a judgment about causation (all categories of evidence left blank in Table 1-1).

⁴ Relevant evidence in one or more categories was identified but was judged to be insufficient to indicate whether or not a causal relation exists (no category of evidence checked as supporting causation in Table 1-1: exceptions are this designation under biologic plausibility for erythema multiforme and hemolytic anemia).

⁵ The available evidence, on balance, does not indicate a causal relation (one or more categories of evidence checked as not supporting causation in Table 1-1, with evidence supporting causation being either absent or outweighed by other evidence).

⁶ The available evidence, on balance, tends to support a causal relation (one or more categories of evidence checked as supporting causation in Table 1-1, with evidence checked as insufficient or not supporting causation being absent or outweighed by the other evidence).

⁷ Defined in controlled studies reviewed as encephalopathy, encephalitis, or encephalomyelitis.

⁸ The available evidence, on balance, supports a causal relation and the evidence is more persuasive than in level 4 above (the categories of evidence are coded similarly to 4 above, with evidence checked as insufficient or not supporting causation in Table 1-1 being absent or fewer than in level 4).

Appendix 8B. Summary of Conclusions From Institute of Medicine Study of Adverse Events Associated With Childhood Vaccine						
Category	DT/Td/T	Measles ^a	Mumps ^a	OPV/IPV ^b	Hepatitis B	H. influenzae type b
1. No Evidence Bearing on a Causal Relation			Neuropathy Residual seizure disorder	Transverse myelitis (IPV) Thrombocytopenia (IPV) Anaphylaxis (IPV)		
2. The Evidence is Inadequate to Accept or Reject a Causal Relation	Residual seizure disorder other than infantile spasms Demyelinating diseases of the central nervous system Mononeuropathy Arthritis Erythema multiforme	Encephalopathy Subacute sclerosing panencephalitis Residual seizure disorder Sensorineural deafness (MMR) Optic neuritis Transverse myelitis Guillain-Barré syndrome Thrombocytopenia Insulin-dependent diabetes mellitus	Encephalopathy Aseptic meningitis Sensorineural deafness (MMR) Insulin-dependent diabetes mellitus Sterility Thrombocytopenia Anaphylaxis ^d	Transverse myelitis (OPV) Guillain-Barré syndrome (IPV) Death from SIDS ^c	Guillain-Barré syndrome Demyelinating diseases of the central nervous system Arthritis Death from SIDS ^c	Guillain-Barré syndrome Transverse myelitis Thrombocytopenia Anaphylaxis Death from SIDS ^c
3. The Evidence Favors Rejection of a Causal Relation	Encephalopathy ^c Infantile spasms (DT only) ^f Death from SIDS (DT only) ^{f, g}					Early onset H. influenzae type b disease (conjugate vaccines)
4. The Evidence Favors Acceptance of a Causal Relation	Guillain-Barré syndrome ^h Brachial neuritis ^h	Anaphylaxis ^d		Guillain-Barré syndrome (OPV)		Early onset Hib disease in children ages 18 months or older who receive their first Hib immunization with unconjugated PRP vaccine
5. The Evidence Establishes a Causal Relation	Anaphylaxis ^h	Thrombocytopenia (MMR) Anaphylaxis (MMR) ^d Death from measles vaccine-strain viral infection ^{c,i}		Poliomyelitis in recipient or contact (OPV) Death from polio vaccine-strain viral infection ^{c,i}	Anaphylaxis	

Source: Stratton, K.R.; Howe, C.J.; Johnston, R.B., eds. *Adverse Events Associated with Childhood Vaccines*. Washington, DC: National Academy Press; 1994.

^a If the data derive from a monovalent preparation, then in the committee's judgment, the causal relation extends to multivalent preparations. If the data derive exclusively from MMR, that is so indicated by (MMR). In the absence of any data on the monovalent preparation, in the committee's judgment, the causal relation determined for the multivalent preparations does not extend to the monovalent components.

^b For some adverse events, the committee was charged with assessing the causal relation between the adverse event and only oral polio vaccine (OPV) (paralytic and nonparalytic poliomyelitis) or only inactivated polio vaccine (IPV) (anaphylaxis and thrombocytopenia). If the conclusions are different for OPV than for IPV for the other adverse events, that is so noted.

^c This table lists weight-of-evidence determinations only for deaths that are classified as SIDS and deaths that are a consequence of vaccine-strain viral infection. However, if the evidence favors the acceptance of (or establishes) a causal relationship between a vaccine and an adverse event, and that adverse event can be fatal, then in the committee's judgment, the evidence favors the acceptance of (or establishes) a causal relation between the vaccine and death from the adverse event. Direct evidence regarding death in association with a vaccine-associated adverse event is limited to tetanus-diphtheria toxoid for adult use (Td) and Guillain-Barré syndrome, tetanus toxoid and anaphylaxis, and OPV and poliomyelitis. Direct evidence regarding death in association with a potentially fatal adverse event that itself is causally related to the vaccine is lacking for measles vaccine and anaphylaxis, MMR and anaphylaxis, OPV and Guillain-Barré syndrome, hepatitis B vaccine and anaphylaxis, and *H. influenzae*

type b unconjugated PRP vaccine and early-onset *H. influenzae* type b disease in children ages 18 months or older who receive their first Hib immunization with unconjugated PRP vaccine. See Chapter 10 for details.

^d The evidence that establishes a causal relation for anaphylaxis derives from MMR. The evidence regarding monovalent measles vaccine favors acceptance of a causal relation, but is less convincing, mostly because of incomplete documentation of symptoms or the possible attenuation of symptoms by medical intervention.

^e The evidence derives from studies of diphtheria-tetanus toxoid for pediatric use (DT). If the evidence favors rejection of a causal relation between DT and encephalopathy, then in the committee's judgment, the evidence favors rejection of a causal relation between Td and tetanus toxoid and encephalopathy.

^f Infantile spasms and SIDS occur only in an age group that receives DT but not Td or tetanus toxoid.

^g The evidence derives mostly from DPT. Because there are supportive data favoring rejection of a causal relation between DT and SIDS as well, if the evidence favors rejection of a causal relation between DPT and SIDS, then in the committee's judgment, the evidence favors rejection of a causal relation between DT and SIDS.

^h The evidence derives from tetanus toxoid. If the evidence favors acceptance of (or establishes) a causal relation between tetanus toxoid and an adverse event, then in the committee's judgment, the evidence favors acceptance of (or establishes) a causal relation between DT and Td and the adverse event as well.

ⁱ The data come primarily from individuals proven to be immunocompromised.

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